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METABOLIC STUDIES IN PATIENTS WITH CANCER OF THE GASTROINTESTINAL TRACT. II. HEPATIC DYSFUNCTION *

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IN a previous communication [1] it was demonstrated that about 85 per cent of patients with cancer of the gastrointestinal tract had abnormally low plasma levels of vitamin A. In the majority of these patients the levels were considered to be due to an inability of the livers of the patients to store the vitamin or to distribute it properly. It thus became desirable to study in greater detail the hepatic function of patients having cancer of the gastrointestinal tract; to correlate, if possible, the existence of hepatic dysfunction with the presence of the cancer; and finally, to note what relation the hepatic function might bear to the ability of patients to withstand operative procedures and to their postoperative course.

It was believed that an estimation of liver function in each patient could be obtained from the results of tests which measure the ability of the liver to synthesize, store, conjugate and excrete metabolites. Such studies were made of four groups of individuals: (*a*) normal adults, (*b*) patients with atrophic gastritis and leukoplakia of the oral mucosa, (*c*) patients with cancer of the gastrointestinal tract, and (*d*) individuals whose neoplasm had been successfully removed by surgery.

The existence of hepatic dysfunction in patients with cancer of the gastrointestinal tract is especially important because they are frequently subjected to prolonged anesthesia and to extensive surgical procedures which, by themselves, are injurious to normal livers.[2, 3] Further injury to an already damaged organ may give rise to serious problems in postoperative care.

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Clinical Material

Twenty-five normal individuals were studied as controls to establish the normal incidence of hepatic dysfunction as measured by the tests employed in this investigation. The subjects were adults of both sexes, from 20 to 65 years of age, and all apparently in good health.

The clinical material studied consisted of four groups of patients. The first group included 62 patients with cancer of the alimentary tract. Five of these had cancer of the esophagus, 39 cancer of the stomach, and 18 cancer of the large intestine. The presence of a malignant epithelial neoplasm was established by one or more of the usual methods—namely, roentgenography, biopsy, endoscopy, or laparotomy. Forty-seven of the patients provided an opportunity for gross examination of the liver, either at operation or autopsy. In 15 instances metastatic nodules in the liver were found, but in none were they sufficiently extensive to suggest the possibility of anatomical impairment of hepatic function. Twelve of the patients with gastric cancer were employed only for a study of the cause of the hypoproteinemia associated with this disorder.

The patients with cancer of the esophagus and stomach received preoperatively liberal, well-balanced, hospital diets. However, three of the five patients with esophageal neoplasm were fed through gastrostomy tubes but these also were considered to receive adequate nutrition. Most of the individuals with cancer of the large bowel received preoperatively diets low in meat and rich in carbohydrate. Considerable vitamin supplements were not administered preoperatively to any of the patients.

Deep roentgen therapy was administered preoperatively to the pelvic region of 15 of the 18 patients with cancer of the large bowel.

The second group comprised 19 individuals whose gastrointestinal neoplasm had been surgically removed. In 12, the lesion originally was of the stomach, and in 7, of the large bowel. At the time of laparotomy a hepatic metastasis * was believed to be present in only one of 19, and that patient is now alive five years after operation. The studies were made from three months to 10 years after operation, and at that time no evidence of neoplastic disease was found.

The third group consisted of eight patients with atrophic gastritis. In all, the presence of the lesion was proved by gastroscopic examination, and all had symptoms referable to their disease.

The fourth group of patients represented 21 routine admissions to the Head and Neck Service of the hospital. All had leukoplakia of the oral mucosa and none had either cancer or syphilis.

No patient in any of the groups studied had any evidence of primary disease of the liver such as cirrhosis or hepatoma.

* This metastatic nodule was not biopsied.

Methods

Liver function studies were not made on any patient until an adequate diet had been taken for at least two days. All the venepunctures were done in the morning when the patients were fasting. The observations on the patients with cancer of the gastrointestinal tract always were made preoperatively, and in many cases postoperatively also.

The procedures employed were as follows:

1. Plasma Prothrombin. The so-called "bedside" technic of Warner, Brinkhouse, and Smith [4] was employed. The values obtained have been found here and elsewhere to check very closely with the actual prothrombin levels as determined by the two-stage titration procedure.

2. Serum Bilirubin. The measurement of serum bilirubin was made by the method of Soffer and Paulson.[6] The extraction of bilirubin with acetone may not be quantitative, and this source of error would result in low values.

3. Serum Proteins. The falling drop technic of Weech [7] was employed, and the serum albumin and globulin by the technic described by Robinson et al.[8]

4. Vitamin A. The method described in the previous communication [1] was used.

5. Urinary Excretion of Glucuronates. These compounds were measured by the technic of Maugham et al.[9]

6. Mean Corpuscular Volume of Erythrocytes. This was determined in whole citrated-oxalated blood as described by Wintrobe.[10]

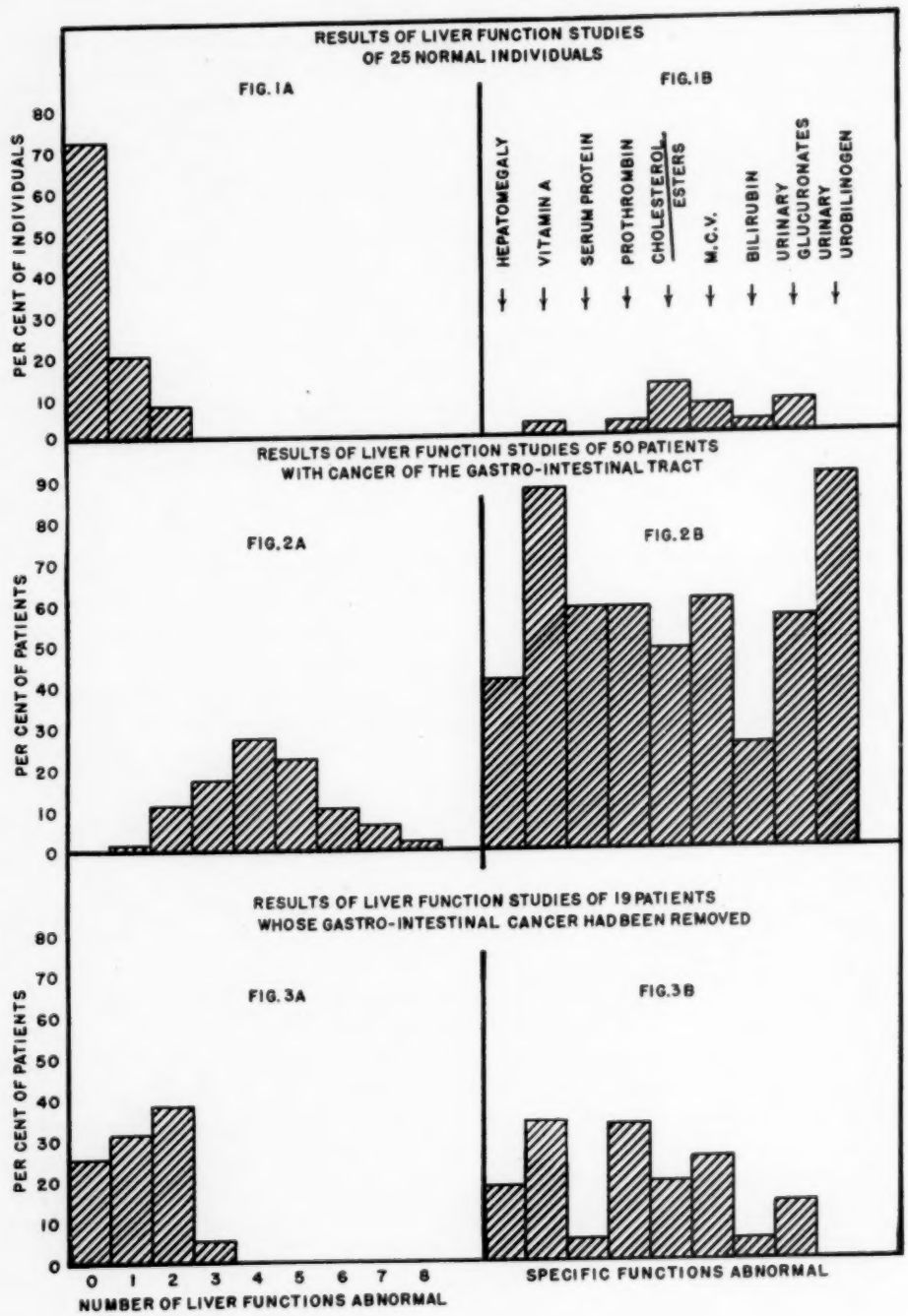
7. Urinary and Fecal Excretion of Urobilinogen. The method of Watson [11] was used.

8. Serum Cholesterol and Cholesterol Esters. These were measured in the serum by the method of Schoenheimer and Sperry.[12]

Hepatic abnormality was considered to be present when: (1) the plasma prothrombin level was less than 85 per cent of the normal; (2) the serum bilirubin was above 1.0 mg. per cent; (3) the total serum protein content was less than 6.6 grams per cent, and the albumin was less than 4.0 grams per cent associated with a globulin of more than 2.0 grams per cent; (4) the plasma level of vitamin A was less than 132 U.S.P. units in males and 103 U.S.P. units in females; (5) the urinary excretion of glucuronates was less than 300 mg. per day; (6) the mean corpuscular volume of erythrocytes was greater than 94 μ^3; (7) the free cholesterol was more than 33 per cent of the total; (8) the urinary excretion of urobilinogen was more than 2.0 mg. per day when the fecal output of the pigment was normal; and (9) hepatomegaly was demonstrable.

Results

The studies described in this communication may be grouped under two headings: (*A*) The results of liver function studies in normal individuals and


RESULTS OF LIVER FUNCTION STUDIES
OF 25 NORMAL INDIVIDUALS
FIG. 1A
FIG. 1B
PER CENT OF INDIVIDUALS
HEPATOMEGALY
VITAMIN A
SERUM PROTEIN
PROTHROMBIN
CHOLESTEROL ESTERS
M.C.V.
BILIRUBIN
URINARY GLUCURONATES
URINARY UROBILINOGEN
RESULTS OF LIVER FUNCTION STUDIES OF 50 PATIENTS
WITH CANCER OF THE GASTRO-INTESTINAL TRACT
FIG. 2A
FIG. 2B
PER CENT OF PATIENTS
RESULTS OF LIVER FUNCTION STUDIES OF 19 PATIENTS
WHOSE GASTRO-INTESTINAL CANCER HAD BEEN REMOVED
FIG. 3A
FIG. 3B
PER CENT OF PATIENTS
NUMBER OF LIVER FUNCTIONS ABNORMAL
SPECIFIC FUNCTIONS ABNORMAL

in patients with cancer of the gastrointestinal tract, and (*B*) Evidence to explain the abnormal functions discovered in those patients.

A. The Results of Liver Function Studies in Normal Adults and in Patients with Cancer of the Gastrointestinal Tract.

1. Normal Adults. Twenty-five individuals were studied and the results are presented in figure 1, table 1. None had hepatomegaly or decreased

TABLE I

Results of Liver Function Studies on Normal Individuals

Individual	Sex	Age	Diet	Hepatomegaly	Plasma Vitamin A, U.S.P. units per cent	Plasma Carotene, mg. per cent	Plasma Prothrombin, per cent	Serum Protein, gm. per cent	Free Cholesterol/ Cholesterol Esters, mg. per cent	Mean Corpuscular Volume, u^3	Serum Bilirubin, mg. per cent	Urine Glucuronate Excretion, mg. per day
J. A.	M	28	A*	No	150	0.22	100	7.3	70.2/140.1	91	.50	816
D. T.	F	22	A	No	152	0.27	100	7.2	49.5/125.7	92	.45	340
A. B.	F	23	A	No	170	0.195	100	7.7	48.9/101.1	84	.60	423
A. R.	F	21	A		143	0.17	100	7.4	48.3/103.9	88	.90	342
M. H.	F	26	A	No	*92*	0.40	100	6.8	63.9/149.9	92	.50	464
N. N.	F	22	A	No	112	0.12	100	7.4	56/124.5	[illegible]	.50	
L. W.	M	28	A	No	162	0.255	100	7.0	*63.6/115.2*	92	.75	386
H. F.	F	41	A	No	185	0.25	100	6.6	58.1/153.4	94	.50	1095
A. G.	F	30	A	No	115	0.30	100	7.8	44.2/104.6	77	.58	446
M. P.	F	37	A	No	190	0.145	100	7.2	42.4/116.9	93	.45	675
V. W.	F	24	A	No	104	0.10	100	7.0	46.8/123.5	*96*	.75	362
N. T.	M	50	A	No	140	0.08	100	7.8	74/188	90	.75	565
N. Y.	M	27	A	No	178	0.13	100	7.2	62.2/129.4	90	.45	649
M. D.	M	29	A	No	163	0.19	100	7.1	53.2/129.8	94	.45	414
K. S.	F	35	A		152	0.16	100	6.8	61/130	76	.90	326
P. R.	M	32	A	No	200	0.32	100	7.0	49/120.9	83	.50	362
W. D.	M	60	A	No	220	0.23	100	7.2	72.7/178.4	94	.65	*280*
S. E.	F	24	A	No	150	0.38	100	7.0	*60.6/120.9*	93	*1.70*	383
G. R.	F	65	A	No	250	0.60	100	6.9	*125.3/224.6*	92	.60	*289*
A. S.	F	25	A	No	150	0.52	94	6.8	63.5/174.9	93	.65	356
B. L.	F	68	A	No	140	0.11	*67*	6.9	44.8/113.8	77	.65	770
J. S.	M	61	A	No	225	0.10	100	7.3	70.2/208.8	90	.60	308
C. B.	F	50	A	No	268	0.215	100	7.2	62.9/163.1	*98*	.65	
A. G.	F	28	A	No	105	0.32	97	7.0	70/148	90	.90	340
E. W.	F	50	A	No	105	0.35	90	7.2	146/349	75	.65	348

* A = Adequate.

concentrations of serum protein. Abnormal values of serum bilirubin, plasma prothrombin and plasma vitamin A were found once each (4 per cent) in the entire group. Two individuals (8 per cent) had macrocytosis and low urinary excretions of glucuronate. Three (12 per cent) had abnormally high levels of free cholesterol in the serum. However, only two of the 25 individuals had as many as two hepatic abnormalities.

2. Patients with Gastrointestinal Cancer. The results of studies of patients with gastrointestinal cancer were in sharp contrast to those obtained in normal individuals. The findings indicated that all of the group of 50 patients examined had one or more abnormal finding (figure 2, table 2).

TABLE II

Results of Liver Function Studies in Patients Bearing Cancer of the Alimentary Tract

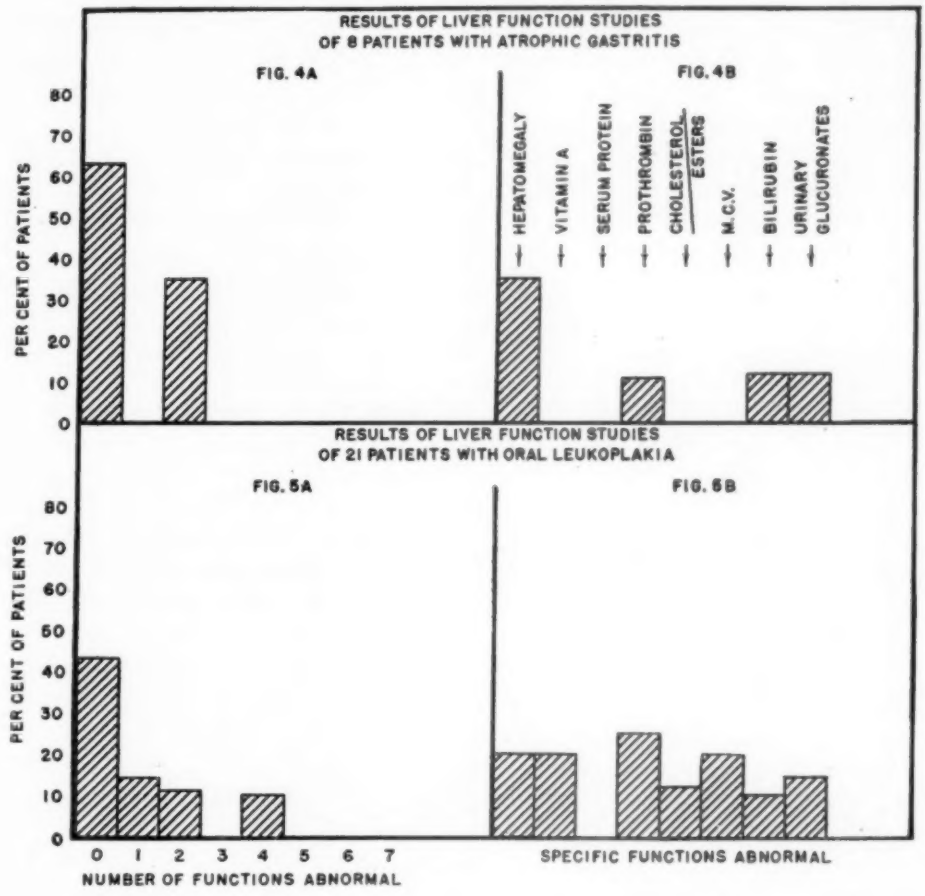
Patient	Sex	Age	Diet*	Site of Cancer	Operation	Liver Metastases	Wound Diarruption	Transfusion Reaction	Achlorhydria	Hepatomegaly	Plasma Vitamin A, U.S.P. units per cent	Plasma Carotene, mg. per cent	Plasma Prothrombin, per cent	Serum Protein, gm. per cent	Free Cholesterol/ Cholesterol Esters, mg. per cent	Mean Corpuscular Volume, u³	Serum Bilirubin, mg. per cent	Urine Glucuronate Excretion, mg. per day	Urinary Urobilinogen, mg. per day
J. A.	M	35	D	Esoph.	Yes	Yes			No	*Yes*	*92*	0.06	*74*	*5.7*	52/112	92	0.38		
L. B.	M	54	A	Colon	Yes	No	Yes			No	*87*	0.11	91	*5.6*		*102*	*1.1*		
K. B.	F	51	D	Stom.	No	?			No	No	*69*	0.145	*81*	7.3	89/220	*98*	*1.6*	*223*	0.25
G. B.	M	40	A	Esoph.	Yes	No				No	*48*	0.07	100	6.8	*55/45*	84	0.85	326	
D. B.	F	65	D	Stom.	Yes	No			Yes	No	*75*	0.05	100	*6.5*	61/146	91	0.25	*163*	
E. B.	M	63	A	Stom.	Yes	No			Yes	No	*83*	0.17	100	*6.3*		85	0.80	*194*	
F. C.	M	42	A	Stom.	Yes	No				No	*29*	0.10	94	*4.8*	*41/58*	80	0.60	450	*3.4*
B. C.	M	55	A	Colon	Yes	No		Yes		No	*65*	0.085	*84*	*5.9*	*56/91*	80	0.7		
D. C.	M	64	A	Stom.	Yes	No			Yes	*Yes*	*107*	0.09		*5.7*	*52/89*	85	0.33	*277*	
P. L.	M	51	A	Stom.	Yes	No			No	No	139	0.075	*80*	7.6	66/174	82	0.60	*224*	
I. D.	M	54	A	Stom.	Yes	No			Yes	*Yes*	179	0.045	100	6.9	*100/140*	*100*	0.50	*208*	
F. F.	M	62	A	Stom.	Yes	No	Yes	Yes	Yes	*Yes*	*67*	0.065	*75*	*6.4*	49/114	80	0.45	*173*	
T. F.	M	67	A	Stom.	Yes	No			Yes	*Yes*	*120*	0.12	*83*	*6.2*	46/103	*100*	0.60	*98*	
D. G.	M	72	A	Rect.	No	?				No	138	0.115	100	*6.4*					
L. G.	M	55	A	Colon	Yes	No				No	*98*	0.16	*75*	7.2	61/135	78	0.50	*117*	
P. G.	M	53	D	Stom.	Yes	No			Yes	No	138	0.095	97	*6.0*	29/62	*100*	*1.15*	532	
J. G.	M	52	D	Stom.	Yes	No			Yes	No	*125*	0.13	88	7.3		92	0.4	447	*4.8*
J. K.	M	47	A	Colon	Yes	No				No	*108*	0.21	100	*5.8*	51/140	*95*	*1.0*	*187*	
E. K.	F	50	A	Stom.	Yes	No				No	*76*	0.055	*75*	*5.6*	47/100	*114*	0.45	*145*	
M. K.	M	72	A	Stom.	Yes	No			Yes	No	*74*	0.075	*68*	6.7	*77/140*	*111*	0.40	*214*	
G. B.	F	60	A	Colon	Yes	No	Yes	Yes		*Yes*	*81*	0.225	*56*	*6.0*	87/190	*110*	0.60	*181*	*5.6*
I. C.	F	38	A	Colon	Yes	No	Yes	Yes		*Yes*	*54*	0.075	100	*4.8*	*78/128*	*105*	0.50	376	*12.5*
G. F.	M	30	A	Stom.	Yes	Yes		Yes		*Yes*	*38*	0.06	*35*	*5.5*	*106/76*	*100*	*7.5*	377	*4.5*
D. H.	M	57	A	Colon	No					No	*112*	0.07	*62*	7.3	*72/79*	*101*			
L. L.	M	72	A	Stom.	Yes	No			Yes	*Yes*	*31*	0.11	90	*4.9*	58/147	*110*	*4.5*		
N. L.	F	44	A	Colon	Yes	Yes				*Yes*	*72*	0.055	*84*	6.8	*75/140*	*105*	0.68	*170*	
M. M.	F	63	D	Stom.	No	?			Yes	No	147	0.27	100	*6.5*		*100*	*1.0*	*156*	
M. M.	F	68	A	Colon	No	Yes				*Yes*	*98*	0.15	*78*	*6.3*	*177/348*	*102*	0.88	*167*	*5.75*
V. N.	M	66	D	Stom.	Yes	Yes			No	No	*48*	0.06	*44*	*5.3*	50/100	90	*5.5*	570	
A. O.	F	64	D	Colon	No	Yes				*Yes*	*44*	0.41	100	*6.0*	*104/168*	*100*	*1.3*	600	
M. P.	M	48	A	Stom.	Yes	Yes			Yes	No	*93*	0.18	100	7.2	*50/96*	93	0.9	*144*	
F. P.	M	57	A	Stom.	Yes	No				*Yes*	*75*	0.075	*67*	*6.5*		*106*	0.45	*142*	
L. P.	M	50	A	Stom.	Yes	Yes			No	*Yes*	*64*	0.055	*80*	7.8	*84/145*	*98*	0.63	585	
J. S.	M	50	A	Sigm.	Yes	No				*Yes*	*110*	0.05	*75*	7.8		*130*	0.38		
O. S.	M	43	A	Colon	Yes	Yes				No	*112*	0.12	*75*	*6.4*	53/111	*104*	0.4		
F. T.	F	45	A	Colon	No	?				No	*70*	0.17	92	*6.0*	31/62	80	0.45	*17*	
S. T.	M	37	A	Stom.	Yes	No			Yes	No	*73*	0.175	*67*	7.1	48/102	80	0.70	435	*30*
F. W.	M	67	A	Stom.	Yes	Yes				No	*68*	0.165	*70*	7.1		*120*	0.85	375	
L. L.	M	55	A	Colon	Yes	No			Yes	No	*32*	0.12	*76*	*6.2*	*54/96*	80	0.45	450	
W. C.	M	66	A	Stom.	Yes	No				*Yes*	*95*	0.27	95	*5.8*	43/94	91	0.45	478	
R. B.	M	56	D	Stom.	Yes	No			Yes	No	*48*	0.07	100	6.8	*48/52*	*110*	0.75	357	
W. V.	M	40	D	Esoph.	Yes	No				No	*93*	0.07	*85*	6.6	*60/80*	*102*	0.6	*248*	
J. E.	F	48	A	Stom.	Yes	No			Yes	*Yes*	*60*	0.21	*56*	7.1	*51/78*	*100*	0.63	378	
D. R.	M	69	A	Colon	Yes	No				No	*30*	0.13	*76*	6.8	*60/78*	84	0.60	*54*	
D. Q.	M	52	A	Stom.	Yes	No			Yes	*Yes*	*37*	0.50	*56*	*5.7*		*100*	0.70		
R. J.	F	45	D	Esoph.	Yes	No				No	*65*	0.085	98	7.2	52/124	*112*	*1.45*	364	
K. P.	M	58	A	Rect.	Yes	No	Yes	Yes		*Yes*	*122*	0.105	*69*	*5.7*	*59.5/95*	*110*	*2.20*	496	
D. B.	M	62	A	Recto-sigm.	Yes	No		Yes		No	*125*	0.095	98	7.7	61/252	90	*1.15*		
D. W.	M	50	A	Stom.	Yes	Yes			No	*Yes*	*98*	0.245	100	7.1	55/123	*103*	0.90	*90*	
F. W.	M	27	D	Esoph.	Yes	No			No	*Yes*	*68*	0.195	*53*	*6.0*	76/165	80	0.63	*169*	*3.6*

* A = Adequate.
D = Deficient.

One patient (2 per cent) had but one abnormality; four (12 per cent) had two; nine (18 per cent) had three; 14 (28 per cent) had four; 11 (22 per cent) had five; five (10 per cent) had six; and four (8 per cent) had seven or more.

Of the 50 patients, 21 (42 per cent) had hepatomegaly, 29 (58 per cent) had reduced levels of serum protein, and 45 (90 per cent) had low plasma levels of vitamin A. The concentration of prothrombin was reduced in the

plasma of 28 of the 48 patients examined (58 per cent) and the serum bilirubin elevated in 12 of the 47 (24 per cent) instances in which it was measured. Twenty-nine of 49 patients (60 per cent) had abnormally high MCV values and 20 of the 43 (45 per cent) had ratios of free to esterified



cholesterol in the serum greater than 1 : 2. The daily urinary excretion of glucuronates was reduced significantly in 23 of 41 (55 per cent) and that of urobilinogen increased in eight of nine (89 per cent) studied.

B. Experiments to Determine the Cause of the Hepatic Insufficiency in Patients with Gastrointestinal Cancer.

The most obvious explanations of the results of the tests of liver functions in the 50 patients with gastrointestinal cancer are: (1) the replacement of their normal liver tissues by metastases from the gastrointestinal neoplasm; (2) malnutrition of the patient and consequently of the liver cells;

(3) the coexistence of the extrahepatic cancer; and (4) a combination of these factors.

1. Hepatic Metastases: It does not seem probable that the findings could have been due to metastatic disease of the liver. Exploratory laparotomy was performed in 41 of the 50 patients, and in only 13 of the 41 patients were any metastases to the liver found. The extent of the involvement in 11 of the 13 instances was considered to be minimal. In only two was there enough cancer tissue in the liver apparently to interfere with the function of that organ by compression of either the vascular or biliary circulation.

2. Malnutrition of the Patients and Consequently of the Liver Cells. Since gastrointestinal disease was present, the possibility of simple malnutrition was considered. The fact has been shown repeatedly that a long continued inadequate diet will deplete the hepatic stores of labile protein,[13, 14] glycogen,[15] vitamins [16] and antianemia principles.[17] These depleted livers are readily susceptible to further damage by toxic agents,[2, 18, 19] and may become inefficient in the performance of other functions such as the excretion of bilirubin and fabrication of prothrombin.

The dietary histories of the 50 patients with gastrointestinal cancer revealed that only 12 had been on diets deficient in calories, proteins, or vitamins. The dietary intake of the other 38 was considered to be adequate by accepted standards. Nevertheless, the occurrence of hepatic dysfunction as manifested by the existence of hypoproteinemia, low plasma levels of vitamin A and prothrombin, and macrocytosis was as common among the 38 patients who had been on adequate diets as among the 12 whose diets were considered grossly deficient.

Of the 12 patients on inadequate diets, 87 per cent had low plasma levels of vitamin A, 58 per cent had hypoproteinemia and macrocytosis, and 42 per cent had hypoprothrombinemia. Likewise, of the 38 patients on apparently adequate diets, 87 per cent had low plasma levels of vitamin A, 58 per cent had hypoproteinemia, 64 per cent had hypoprothrombinemia, and 60 per cent had macrocytosis.

In order to determine whether the low plasma levels of vitamin A and prothrombin of the patients with gastrointestinal cancer were due to an inadequate ingestion of vitamins A and K, or to some other reason, several patients were given large amounts of those vitamins and measurements of vitamin A and prothrombin were subsequently made in their plasma.

(*a*) *Vitamin A.* Eight unselected patients with cancer of the gastrointestinal tract and low plasma levels of vitamin A were given from 50,000 to 150,000 U.S.P. units of vitamin A for from 7 to 20 days. These amounts of vitamin A are sufficient to raise the low levels of the vitamin in the plasma of individuals on low vitamin A diets.[1, 20, 21] The vitamin was administered orally to one patient, parenterally to six, and both orally and parenterally to one. Only one of these patients was known to have been on a deficient diet. After the administration of the vitamin, the plasma level

rose in two of eight instances. In the other six the plasma levels of vitamin A were from 5 to 33 per cent less than they had been before the administration of the vitamin supplements (table 3).

TABLE III

Results of the Administration of Vitamin A to Patients with Cancer of the Gastrointestinal Tract

Patient	U.S.P. Units of Vitamin A Administered	Mode of Administration	Plasma Vitamin A	
			Pre-Therapy	Post-Therapy
J. D.	900,000	i.m.	96	92
F. F.	1,050,000	i.m.	128	48
E. B.	630,000	p.o.	116	164
M. H.	500,000 400,000	p.o. i.m.	108	72
F. W.	800,000	i.m.	88	76
D. W.	2,000,000	i.m.	92	68
F. P.	750,000	i.m.	88	64
M. S.	500,000	i.m.	100	176

(*b*) *Vitamin K.* In a similar manner six unselected patients with gastrointestinal cancer and with low plasma levels of prothrombin were given daily 2 mg. of synthetic vitamin K * parenterally for from two to three days. It has been shown that 1.0 mg. of vitamin K will cause a substantial rise in the low plasma prothrombin levels when a dietary deficiency or malabsorption of the substance is present.[22] However, the administration of from four to six times the therapeutic dose to the six patients studied failed to induce any significant change in their concentrations of plasma prothrombin (table 4). After the vitamin K therapy, the prothrombin levels of the six patients studied rose in three only from 7 to 18 per cent, fell in one, and was not altered in two patients.

TABLE IV

Results of Parenteral Administration of Synthetic Vitamin K to Patients with Cancer of the Gastrointestinal Tract

Patient	Prothrombin Level	
	Pre-Vitamin K, per cent	Post-Vitamin K, per cent
W. C.	55	65
J. B.	72	77
W. B.	59	69
D. R.	58	59
L. D.	81	54
S. H.	49	49

(*c*) *Serum protein.* Hypoproteinemia was found in 29 of the 50 patients studied, and in only seven instances could histories of diets deficient in protein be elicited. It is possible, nevertheless, that the information obtained concerning the protein intake was inaccurate, and that the frequent

* 2 methyl 1, 4 naphthoquinone.

occurrence of hypoproteinemia must be regarded not as a result, but as a cause of hepatic insufficiency.

The fact has been demonstrated repeatedly [23] that the albumins are manufactured principally by the liver cells. Hence, low serum levels of albumin in the presence of normal concentrations of serum globulin would be more likely to reflect an inability of the liver to synthesize albumin than to indicate an inadequate protein intake. For that reason it was deemed important to determine whether or not the hypoproteinemia found in patients with cancer of the gastrointestinal tract was due chiefly to hypoalbuminemia.

Determinations of serum albumin and globulin were made in 12 patients, only three of whom had been on grossly inadequate diets. Of these 12 patients, 11 had concentrations of serum protein under 6.5 per cent, and of the 11, 10 had concentrations of serum albumin under the accepted low level of 4.0 grams per cent. In only two of the 10 patients were these levels of hypoalbuminemia associated with levels of serum globulin of less than 2.0 grams per cent (table 5), and those two patients had been on deficient

TABLE V

The Concentrations of Total Protein, Albumin and of Globulin in the Serum of Patients with Cancer of the Gastrointestinal Tract

Patient	Diet	Total Serum Protein, gm. per 100 ml.	Serum Albumin, gm. per 100 ml.	Serum Globulin, gm. per 100 ml.
F. B.	Adequate	6.60	4.26	2.34
D. S.	Adequate	6.25	3.40	2.85
A. N.	Adequate	6.19	3.72	2.47
S. G.	Adequate	5.90	2.85	3.15
F. K.	Adequate	5.90	3.32	2.58
J. M.	Adequate	6.45	3.90	2.55
F. R.	Adequate	5.36	3.26	2.10
H. G.	Adequate	5.98	3.96	2.02
D. M.	Adequate	5.45	3.04	2.41
J. R.	Inadequate	4.83	3.36	1.47
E. W.	Inadequate	5.70	4.24	1.36
K. P.	Inadequate	4.64	2.92	1.72

diets. Thus, it would appear that the hypoproteinemia found in 11 patients could be explained in 10 instances by a decreased concentration of the albumin fraction, and that in eight of the 10 the hypoalbuminemia was due to an impaired fabrication and not to a decreased dietary intake of protein.

In short, from such experiments as could be performed, it appeared that the frequent occurrence of low plasma levels of vitamin A and prothrombin at least are not due to inadequate diets, but rather to a specific disorder which prevented the normal distribution by the liver of vitamin A or the utilization of vitamin K. Likewise, the occurrence of hypoproteinemia in many of the patients is due probably to an impaired ability of the liver to synthesize albumin and not to an inadequate dietary intake of protein.

Although the evidence at hand indicated that inadequate diets probably could not explain the high incidence of hepatic dysfunction in patients with

gastrointestinal cancer, one could not be satisfied that the normal values used for comparison were valid controls, since the normal subjects differed considerably in age and in economic and dietary background from the patients. Hence, it was important to control further these factors.

Accordingly, measurements were made of the hepatic function of two other groups of patients—one with atrophic gastritis, and the other with leukoplakia of the oral mucosa. The patients of these groups were of an age and dietary and economic background similar to those with gastrointestinal cancer.

TABLE VI

Results of Liver Function Studies in Patients with Atrophic Gastritis

Patient	Sex	Age	Diet	Hepatomegaly	Plasma Vitamin A, U.S.P. units per cent	Plasma Carotene, mg. per cent	Plasma Prothrombin, per cent	Serum Protein, gm. per cent	Free Cholesterol/ Cholesterol Esters, mg. per cent	Mean Corpuscular Volume, μ^3	Serum Bilirubin, mg. per cent	Urine Glucuronate Excretion, mg. per day
L. O.	F	42	D	Yes			90	7.3	*79/138*	80	0.58	455
W. N.	M	57	A	No	169	0.15	100	7.6	70/151	78	0.65	495
D. S.	M	45	A	No	216	0.08		7.8	54/108	74	0.70	522
A. D.	F	40	A	Yes	130	0.09	100	6.8	64/147	90	0.94	*119*
G. K.	M	62	D	No	132	0.08		6.6	85/175	85	0.63	
S. U.	F	50	A	Yes	121	0.14	100	6.9	39/94	83	*1.13*	400
A. S.	F	43	A	No	215	0.20	100	7.8	64/135	81	0.88	686
I. R.	M	62	A	No	138	0.21	96	7.3	88/209	86	0.63	560

In eight patients with atrophic gastritis (figure 4, table 6), a lesion sometimes held to be precancerous,[24] little evidence could be found for the coexistence of hepatic disease. Two of the eight had been on grossly inadequate diets but none had low plasma levels of vitamin A, hypoproteinemia, macrocytosis, or hypoprothrombinemia. Only one patient had an increased level of serum bilirubin, a second had an increased ratio of free to esterified serum cholesterol, and a third had a decreased urinary output of glucuronates. However, it is interesting to note that three of the eight had hepatomegaly. Five of the eight were entirely free of evidence of hepatic insufficiency, and the remaining three patients each had two criteria of liver disease.

Of 21 patients with oral leukoplakia (figure 5, table 7), four of 20 (20 per cent) had hepatomegaly; two of 19 (10 per cent) had hyperbilirubinemia; none of 19 had hypoproteinemia; four of 21 (19 per cent) had low levels of plasma vitamin A; one of four (25 per cent) had an abnormally decreased plasma prothrombin; one of 16 (6 per cent) had an increased ratio of serum cholesterol to cholesterol esters; four of 17 (24 per cent) had a decreased urinary output of glucuronates.

Of the abnormalities considered to indicate hepatic dysfunction, none were found in nine patients with oral leukoplakia; one in seven; two in three; and four in one. Seven of the 21, or 33 per cent, had been on grossly deficient diets.

TABLE VII
Results of Liver Function Studies on Patients with Oral Leukoplakia

Patient	Sex	Age	Diet *	Hepatomegaly	Plasma Vitamin A, U.S.P. units per cent	Plasma Carotene, mg. per cent	Plasma Prothrombin, per cent	Serum Protein, gm. per cent	Free Cholesterol/ Cholesterol Esters, mg. per cent	Mean Corpuscular Volume, u^3	Serum Bilirubin, mg. per cent	Urinary Glucuronate Excretion, mg. per day	Urobilinogen Urine, mg. per day
D. B.	F	55	A	No	192	0.137		7.1		90	.45	300	.34
L. D.	M	7	D	*Yes*	*116*	0.16		7.1 7.5	72/144	85	.80	340	.32
B. B.	F	62	D		160	0.04			70/171	82	.87	363	
A. C.	F	66	A	No	269	0.18		7.2	60/147	*100*	.90	*283*	
T. R.	M	44	A	No			*80*	8.5	79/181	81	.45	582	
J. R.	M	38	D	No	138	0.275		6.9	66/155	90		*290*	
E. M.	M	46	A	No	*85*	0.57		7.8	43/107	80	.25		
F. N.	M	56		*Yes*	*51*	0.22		6.9	68/164	84	.90	436	
W. N.	M	69	A	No	169	0.15	100	7.6	70/151	75	.65	495	
J. S.	M	50	A	No	140	0.21			70/146	77		514	
J. B.	F	70	A	No	170	0.19		7.8		83	.90	379	
A. J.	F	61	D	No				8.2	82/181	82	*3.5*		
E. S.	M	66	D	No	215	0.11	93	6.7	60/151	*97*	.75	324	
A. P.	M	41	D	No	185	0.226		6.6	51/199	86	.45	438	
C. K.	M	63	A	*Yes*	140	0.11		7.7	*76/104*	73	*1.08*	*100*	
H. K.	M	54	A	No	188	0.18		7.0	51/128	73	.58		
A. B.	M	45	A	No	193	0.11		7.1	50/123	87	.90		
J. F.	M	51	A	No	163	0.22		7.4			.75	458	
L. F.	M	80	A	No	*110*	0.11		7.0	60/150	*95*	.63	475	
S. J.	M	54	A	No	331	0.225		7.3		*95*	.70	537	
M. K.	M	46	D	*Yes*	381	0.107	100	7.4	42/191	86	.50	*205*	

* A = Adequate.
D = Deficient.

A comparison of the findings in the patients with leukoplakia and atrophic gastritis with the findings in patients with cancer of the gastrointestinal tract seems to provide sufficient proof that the factors of age, dietary and economic background of the latter group were not responsible for the high incidence of hepatic dysfunction.

3. *The Coexistence of Extrahepatic Cancer.* If the hepatic dysfunction of patients with gastrointestinal cancer is the result of the neoplastic process, then, when the tumors were completely removed, an improvement of hepatic function should be expected. Such improvement only would be possible, however, if too much organic disease had not occurred in the liver and if the process were reversible.

Studies of liver functions were made in 19 patients whose gastrointestinal cancer had been removed successfully. These patients had survived for from three months to 10 years, and were apparently still free of disease. Twelve originally had had cancer of the stomach and seven cancer of the large bowel; of the 19 patients, three had been on grossly deficient diets for at least four months before the liver function studies were performed.

The results obtained by the examination of the hepatic function of these patients (figure 3, table 8) clearly indicate that the incidence and severity of

TABLE VIII

Results of Liver Function Studies on Patients Who Have Had a Cancer of the Alimentary Tract Removed

Patient	Sex	Age	Diet[1]	Hepatomegaly	Site of Cancer	Survival Period Post-Op., months	Plasma Vitamin A, U.S.P. units per cent	Plasma Carotene, mg. per cent	Plasma Prothrombin, per cent	Serum Protein, gm. per cent	Free Cholesterol/ Cholesterol Esters, mg. per cent	Mean Corpuscular Volume, u[3]	Serum Bilirubin, mg. per cent	Urine Glucuronate Excretion, mg. per day
L. B.	F	56	A	No	Stom.	60	*82*	0.28	90	6.7	119/281	89	0.90	359
N. C.	M	61	A	No	Stom.	60	380	0.11	100	8.1		80	0.65	351
J. C.	M	55	D	No	Stom.[2]	12	132	0.10	100	6.9	*66/81*	*95*	0.65	312
A. A.	F	45	A	*Yes*	L. B.	2	160	0.15	*77*	6.7		91	0.75	
I. A.	M	49	A	No	L. B.	70	172	0.08	100	7.7	39/134	74	0.75	322
W. E.	M	47	A	No	Stom.	6	272	0.06	86	7.3	62/128	*96*	0.50	
M. P.	F	40	A	*Yes*	Duo.	12	*90*	0.02	94	*6.2*[4]	43/87	90	0.40	680
E. P.	M	63	D	*Yes*	Stom.	2	*122*	0.13	*56*	7.7	43/89	80	0.65	600
K. T.	M	41	A	No	Stom.	96	*122*	0.10	94	7.0	49/105	90	0.75	544
J. Z.	M	58	A	No	Stom.	120	*80*	0.16	98	7.1	58/118	90	*2.00*	544
A. S.[3]	F	50	A	No	Stom.	60	125	0.13	95	7.5	53/126	90	0.70	330
A. E.	M	68	A	No	L. B.	62	232	0.03	*70*	6.7	*74/143*	*99*	0.75	
M. I.	F	72	A	No	Stom.	16	*62*	0.11	90	7.9	68.5/201		0.90	*189*
G. B.	F	65	A	No	L. B.	4	352	0.18	*63*	7.1	80/217	93	0.75	*220*
H. S.	M	54	A	No	Stom.	40	208	0.12	100	7.1		*95*	0.75	
P. S.	M	48	D	No	Stom.	31	*88*	*0.09*	88	7.6	*57.5/108*	90	0.90	617
I. C.	F	47	A	No	L. B.	8	132	0.12	92	7.7	70/197	89	0.75	775
E. L.	F	48	A	No	L. B.	53	270	0.25	*80*	8.1	71/207			330
A. J.	M	56	A	No	Stom.	15	210	0.07	*74*	7.2		85	0.50	

[1] A—Adequate diet. D—Deficient diet.
[2] Total gastrectomy.
[3] Reported to have metastases to liver at time of operation. No biopsy obtained.
[4] Pancreatic insufficiency.

hepatic dysfunction in this group are much less than those found in the group of patients still bearing gastrointestinal cancer. Of the 19 patients, hepatomegaly was present in three (16 per cent), hyperbilirubinemia and hypoproteinemia each in one (5 per cent), hypoprothrombinemia in six (33 per cent), and low plasma levels of vitamin A in seven (34 per cent). An increased ratio of cholesterol to cholesterol esters was noted in three of 16 (19 per cent) and macrocytosis in four of 17 instances (23 per cent). Reduced excretions of urinary glucuronates were found in only two of 14 patients (14 per cent).

No evidence of hepatic disease was found in five of the 19 patients. Only one of the nine criteria for hepatic dysfunction was found to exist in six patients; two in seven; and three in one (figure 3).

Thus, a comparison of the results of these studies with those of comparable studies made in patients still bearing cancer show striking differences (table 9). Among the patients bearing active cancer of the gastrointestinal tract, the incidence of hepatomegaly is 2.6 times as great as that in the patients with such tumors removed. Likewise, the incidence of low plasma levels of vitamin A is 2.7 times as great; of hypoprothrombinemia, 1.8 times;

TABLE IX

Comparison of the Results of Liver Function Studies Obtained in Normal Individuals and in the Groups of Patients Studied

	Normals	Leukoplakia of the Oral Mucous Membranes	Atrophic Gastritis	Cancer of the Gastrointestinal Tract	Cancer of the Gastrointestinal Tract Removed
Number of Patients	25	21	8	50	19
Hepatomegaly	0%	20%	37.5%	42%	16%
Elevated Serum Bilirubin	4%	10%	12.5%	24%	5%
Decreased Serum Protein	0%	0%	0%	58%	5%
Decreased Plasma Prothrombin	4%	25%	0%	58%	33%
Impaired Cholesterol Esterification	12%	6%	12.5%	45%	19%
Increased MCV of Erythrocytes	8%	20%	0%	60%	23%
Decreased Plasma Vitamin A	4%	19%	0%	90%	34%
Decreased Urinary Excretion of Glucuronates	8%	24%	12.5%	55%	14%

of macrocytosis, 2.5 times; of hyperbilirubinemia 5.0 times; of increased ratios of free to esterified cholesterol, 2.6 times; and finally, of decreased urinary daily output of glucuronates, 6.2 times that found in patients whose tumors had been removed.

In summary, therefore, it appears that no significant hepatic dysfunction exists in patients with atrophic gastritis, that it is pronounced in patients bearing a cancer of the gastrointestinal tract, and it is considerably less prominent among patients whose cancer has been removed successfully.

DISCUSSION

Inasmuch as the liver performs multiple functions, it is reasonable to believe that no single test can measure adequately the efficiency of the whole organ. By the measurement qualitatively, and when possible quantitatively, of various intermediary or end products of liver metabolism and then by the consideration of the results as a whole, it is felt that abnormal function can be detected.

Liver function tests at the best are crude. The exact amount of liver tissue that can be destroyed before an abnormal result of any test can be noted is unknown, but it is probably considerable. Experimentally, it has been shown that from one-half to two-thirds of the liver can be damaged and the organ will still regenerate and return to normal.[25] Disease of the liver may progress to a far advanced stage before symptoms result or changes are produced which indicate hepatic dysfunction.

In this study measurements of liver function were selected arbitrarily. It is, therefore, necessary to consider the evidence which would indicate that the tests employed in this study are adequate measurements of hepatic function.

Prothrombin. There is considerable evidence to show that the liver is the site of prothrombin formation.[26] A fall of the prothrombin level con-

sistently parallels liver injury, and the level of that substance returns to normal as the liver regenerates.[27] Decreased plasma prothrombin levels follow operations,[5] certain anesthesias,[28] trauma to the liver,[29] cirrhosis, obstructive jaundice,[30] and prolonged malnutrition with depleted nutritional stores.[31]

Serum Bilirubin. It is well established that the increase of bilirubin in the plasma parallels the inability of the liver to excrete that pigment. In the absence of increased intravascular lysis, hyperbilirubinemia must signify hepatic impairment.[32]

Total Protein, Albumin and Globulin. The liver is of primary importance in the formation, storage and exchange of plasma protein.[23] Fibrinogen is produced only by the liver cells,[33] and the best available evidence indicates that the albumins, likewise, are formed by that organ.[6]

Abnormal levels of circulating serum or plasma protein are reached only when the protein stores, chiefly in the liver, are decreased. The normal individual, depleted of his protein stores, readily can synthesize albumin, globulin and fibrinogen from a proper mixture of amino acids,[23] but those proteins are deposited first in the liver and other organs, and do not appear in the plasma until the body stores are reëstablished. In a damaged liver the synthesis of protein from amino acids may be altered [34] and the circulating concentrations of plasma protein continue to decrease with further hepatic damage. The disappearance of the hepatic stores of protein with damage to the organ now has been shown by experiments which employ Eck fistula dogs [35] as well as by clinical studies of patients with hepatic cirrhosis.[23]

Vitamin A. There is reason to believe that many patients with hepatic insufficiency have low levels of vitamin A in their plasma. Of 25 patients with unequivocal cirrhosis, 16 had plasma levels of vitamin A below that of the lowest normal.[36] This finding of low plasma levels of vitamin A in hepatic cirrhosis also has been noted by others.[37] Clinical improvement of the patients with cirrhosis usually is associated with an increased amount of vitamin A in the plasma.

Glucuronic Acid. It has been demonstrated that several aromatic compounds normally are conjugated with glucuronic acid and excreted as glucuronates in the urine.[38] This conjugation has been considered by several investigators to be a form of detoxification. The liver is the chief site for this synthesis of glucuronates. The kidney is the only other organ known to produce glucuronates, but its capacity for that production is only from one-tenth to one-sixth that of the liver. Livers injured by phosphorus soon lose their capacity to make glucuronic acid.[39]

Mean Corpuscular Volume. Macrocytosis affects the majority of red blood cells in the anemia associated with cirrhosis of the liver. One-half of 37 patients with hepatic disease were found to have macrocytosis, whereas hypochromic anemia was noted only when the patients suffered simultaneously from chronic blood loss. In all likelihood, this macrocytic anemia is due to an inability of the liver to store the necessary hematopoietic prin-

ciple, for certain livers removed at autopsy from patients with hepatic cirrhosis or necrosis appear to have been ineffectual in the treatment of pernicious anemia.[40]

Urinary Urobilinogen. If the fecal excretion of urobilinogen is within normal limits, the urinary excretion of that substance is considered to be a valuable index of hepatic function. It has been demonstrated that, under normal conditions, most of the urobilinogen absorbed from the gastrointestinal tract into the blood stream is converted by the liver cells into bilirubin.[41, 47] The rate of that conversion, therefore, must be impaired when excessive amounts of urobilinogen appear in the urine.

Cholesterol and Cholesterol Esters. The serum concentration of total cholesterol and the ratio of free to esterified cholesterol in the normal healthy individual is maintained within rather narrow limits. From the best evidence at hand, it appears that the esterification of this sterol is accomplished chiefly in the liver.[43] Therefore, changes in the ratio of free to esterified cholesterol are of great significance.

In conclusion, it would appear that the tests employed in this study when considered as a group provide an adequate index of hepatic function. It is recognized that this study is incomplete and the use of other measurements of hepatic function, such as the excretion of bilirubin or bromsulphthalein, and the conversion of galactose would have been desirable, but at the time of this study such methods were not available in this laboratory.

Even in the normal individual the administration of anesthetics [2] and the manipulation of the liver [3] have been shown to induce hepatic insufficiency. Therefore, it could be expected that in patients who already have physiologically damaged livers such procedures would result in more marked, and less well-tolerated, hepatic dysfunction. It has been demonstrated that the normal liver will recover completely from the effects of the administration of inhalation anesthetics, but the damaged organ, further impaired by toxic agents, may not return even to its previously reduced functional capacity.[2, 44, 15] Since patients with cancer of the gastrointestinal tract frequently undergo of necessity prolonged anesthesia and handling of the liver, their associated hepatic disease thus would add to the risks entailed by those procedures. Most of the 50 patients herein reported received combinations of large amounts of barbiturates both by mouth and intravenously. These drugs, known to be detoxified by the liver,[48] must impose an added load on an already damaged organ.

The frequent occurrence of hypoproteinemia, whether due primarily to impaired hepatic fabrication or to inadequate dietary intake of protein, has a special significance in these patients because of its direct relationship to delayed wound healing.[46] The process of wound healing is a phenomenon of growth, and the repair and tensile strength of wounds are direct functions of fibroblastic proliferation and collagen formation. Reduction in the labile protein stores alters the formation of collagen and impairs fibroblastic activity

and the growth of the corium.[47] These alterations thus could result in delayed wound healing and even lead to wound disruption. The edema naturally occurring at wound edges is intensified and of longer duration in the presence of hypoproteinemia.[46]

The fact is to be emphasized that hypoproteinemia in patients with hepatic disease is not to be considered a transient phenomenon although originally it might have been due to dietary deficiency or to blood loss. Hypoproteinemia in these patients represents a decrease in labile protein stores, and, because of previous or consequent hepatic damage, the impaired fabrication of plasma proteins must aggravate the hypoproteinemia.

The high incidence of macrocytic anemia in the patients with gastrointestinal cancer, likewise, probably plays an important rôle in their postoperative course. Anemic patients are believed to be less resistant to infections, and it is a common clinical observation that patients with tumors of the alimentary tract frequently manifest infection in the tumor, peritoneal cavity, or wounds as a result of inevitable contamination at the time of operation.[48] To aggravate this already serious situation, the anemia due to hepatic insufficiency is usually refractory to therapy.[49, 50]

Finally, not only does hepatic damage impose an augmented hazard in the patients subjected to anesthetics and operative procedures, but also to the transfusion of blood. This subject is discussed in detail in a subsequent report. Of the 50 patients reported in this communication 42 received transfusions and of these 42, 10 manifested severe hemolytic reactions.

It has been shown that the incidence of hepatic dysfunction is considerably less in patients who had had a neoplasm of the gastrointestinal tract removed. This observation would suggest that the presence of the cancer had resulted in hepatic insufficiency which to a large extent was reversible.

Conclusions

1. Patients with cancer of the gastrointestinal tract show a very high incidence of hepatic dysfunction.

2. The incidence of hepatic dysfunction is considerably less in patients who have had cancer of the gastrointestinal tract removed surgically.

3. The incidence of hepatic dysfunction is considerably less in patients with such lesions as atrophic gastritis and leukoplakia of the oral mucous membranes.

4. The existence of hepatic dysfunction in patients with cancer of the gastrointestinal tract is especially important because of the augmented hazard it imposes on their operative and postoperative course. Delayed wound healing, refractory anemia, hemolytic reactions to transfusion, hypoproteinemia and hypoprothrombinemia may all be associated with and possibly are due to liver insufficiency.

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VITAMIN D IN THE TREATMENT OF INFECTIOUS ARTHRITIS *

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IN 1935 Dreyer and Reed [1] reported clinical improvement among patients who had infectious (rheumatoid, atrophic) arthritis when treated with large doses of vitamin D. Reports which have appeared in the literature are summarized in table 1. Livingston [2] reported that his best results were

TABLE I

Summary of Findings in the Literature Concerning Treatment with Vitamin D in Cases of Infectious Arthritis

Investigators	Patients Treated with Vitamin D	Percentage with Clinical Improvement
Dreyer and Reed[1]	34	73.5
Vrtiak and Lang[5]	20	60
Holbrook and Hill[6]	25	20
Livingston[2]	14	86
Wyatt, Hicks and Thompson[7]	40	20
Farley[8]	27	100
Steck[9]	Not stated	75 to 80
Steinberg[10]	29	34
Abrams and Bauer[3]	18	44
Snyder and Squires[11]	13	69

from the combination of vitamin D therapy and fever therapy. Abrams and Bauer [3] seldom saw objective evidence of improvement accompany clinical improvement in their patients and observed that the beneficial effects of vitamin D were only transitory.

PROCEDURE

Fourteen patients with chronic infectious (rheumatoid, atrophic) arthritis were chosen for study. Their ages were from 17 to 59 years. The infectious arthritis had been present from seven months to seven years. For each patient conservative treatment had been tried, but it was inadequate in controlling the arthritis. Preparations of vitamin D used were "Viosterol —Experimental" (1,000,000 units per gram), a special solution of activated ergosterol, and a crystalline vitamin D in propylene glycol (40,000 U.S.P. units per gram). These were furnished, respectively, by Parke, Davis and Company, Mead Johnson and Company, and the Winthrop Chemical Company. The daily dosage varied from 52,500 units to 386,000 units. The administration of vitamin D was continued from twelve days to fifteen and a half months. If no clinical improvement occurred, its administration was continued for at least one and a half months. Each patient was studied during the administration of vitamin D in regard to subjective and objective

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changes, clinical and laboratory evidence of toxicity, and the duration of improvement following discontinuance of the medication.

Because of the marked variation of symptoms in infectious arthritis, several courses of treatment were given to some of the patients, to be as certain as possible that such improvement as was obtained was due to the vitamin D and not to spontaneous remissions. The 14 patients were given 25 periods of treatment with vitamin D. These patients have been followed for at least one year since the administration of vitamin D was discontinued.

Clinical improvement was evaluated on the basis of the information obtained from the patient in regard to pain, subjective stiffness, fatigue, limbering up, and the amount of aspirin required. Objective improvement was determined on the basis of swelling and tenderness of the joints.

Results

Clinical improvement to the extent of disappearance of 25 to 75 per cent of symptoms occurred in seven patients (50 per cent); four (28.6 per cent) obtained no relief of symptoms; three (21.4 per cent) had partial relief of symptoms during one or more periods of treatment but did not improve during a subsequent trial of treatment with vitamin D.

The 14 patients were given a total of 25 periods of treatment. Eight treatments (32 per cent) resulted in no symptomatic relief; three treatments (12 per cent) resulted in subjective improvement to a degree of 25 per cent; twelve treatments (48 per cent) resulted in improvement to the extent of 50 per cent; and two (8 per cent) resulted in improvement to the extent of 75 per cent (table 2). Objective improvement was not noticed after 11

Table II

Effects of 25 Courses of Therapy with Vitamin D in 14 Cases of Infectious Arthritis

Treatment	Symptomatic Improvement		Vitamin D, units	
	Present	Absent	Maximal Daily Dose	Minimal Daily Dose
25 courses	17	0	386,000	52,500
	0	8	315,000	80,000

treatments (44 per cent); objective improvement to the extent of 25 per cent was noticed after 12 treatments (48 per cent); and improvement to the extent of 50 per cent was noticed after two treatments (8 per cent). There was considerable variation in the readings of the sedimentation rate of erythrocytes and in the concentration of hemoglobin; improvement in these was very inconstant and frequently did not parallel the clinical and objective improvement.

There was no correlation between the amount of improvement and either the daily dose or the total dosage. When improvement occurred it was first

noticed from five days to three weeks after starting the administration of vitamin D.

After the administration of vitamin D was discontinued, one patient maintained the improvement for one and a half years and another for two and a half years, before having a return of the active infectious arthritis. The other patients had a return of symptoms within eight days to two and a half months after administration of the vitamin D was discontinued. In most cases, the symptoms returned and were as severe as they were before vitamin D was given. Three of the patients had transitory exacerbations of the infectious arthritis while taking vitamin D, and in one case the infectious arthritis was more active after the administration of vitamin D was discontinued than when it was started.

The most frequent symptoms of toxicity from vitamin D were loss of appetite, the presence of a sweet taste in the mouth, nausea, vomiting, headache, polydipsia and polyuria. Twelve of the 14 patients had toxic symptoms in at least one period of treatment. Toxic symptoms occurred in 17 of the 25 periods of treatment (table 3).

TABLE III

Relation of Symptoms of Toxicity to Symptomatic Improvement and Daily Dosage during 25 Courses of Vitamin D in 14 Cases of Infectious Arthritis

Treatment	Symptoms of Toxicity		Symptomatic Improvement		Vitamin D. Units	
	Present	Absent	Present	Absent	Maximal Daily Dose	Minimal Daily Dose
25 courses	17	0	12	5	386,000	52,500
	0	8	5	3	315,000	70,000

There was a higher percentage of improvement among those who had toxic symptoms than among those who did not, but it is obvious that toxic symptoms are not necessary to produce improvement, nor will doses of vitamin D sufficient to produce toxicity necessarily produce improvement in a case of infectious arthritis. Some patients tolerate very large doses of vitamin D and others react to small doses. It did appear that patients who had had toxic symptoms from vitamin D usually did not tolerate as much on subsequent trials without producing toxic symptoms.

Studies of the serum calcium were made during 15 of the 25 courses of treatment (table 4). Symptomatic improvement was experienced by all of the patients who had an elevation of serum calcium, but of four patients with a serum calcium of less than 11 mg. per 100 c.c. two experienced improvement and two did not. It is not necessary to produce a high serum calcium in order to obtain improvement of the patient's condition, but such an elevation frequently occurs. Toxic symptoms may occur with or without an elevation of serum calcium and this elevation is no gauge of the toxicity of the vitamin D for the patient.

The blood urea was studied because of the known toxic effects of large

TABLE IV

Relation of Serum Calcium to Symptoms of Toxicity, Symptomatic Improvement and Daily Dosage during 15 Courses of Vitamin D in 11 of 14 Cases of Infectious Arthritis

Treatment	Serum Calcium		Symptoms of Toxicity		Symptomatic Improvement		Vitamin D, Units	
	More than 11 mg. per 100 c.c.	Less than 11 mg. per 100 c.c.	Present	Absent	Present	Absent	Maximal Daily Dose	Minimal Daily Dose
15 courses	11	0	8	3	11	0	386,000	52,500
	0	4	4	0	2	2	210,500	140,000

TABLE V

Relation of Blood Urea to Serum Calcium, Symptoms of Toxicity, Symptomatic Improvement and Daily Dosage during 16 Courses of Vitamin D in 12 of 14 Cases of Infectious Arthritis

Treatment	Blood Urea		Serum Calcium		Symptoms of Toxicity		Symptomatic Improvement		Vitamin D, Units	
	More than 40 mg. per 100 c.c.	Less than 40 mg. per 100 c.c.	More than 11 mg. per 100 c.c.	Less than 11 mg. per 100 c.c.	Present	Absent	Present	Absent	Maximal Daily Dose	Minimal Daily Dose
16 courses	6	0	4	0	5	1	6	0	386,000	105,000
	0	10	6	4	8	2	7	3	280,000	52,500

doses of vitamin D on the kidneys (table 5).[4] The level of blood urea was followed during 16 of the 25 periods of treatment with vitamin D. Readings of more than 40 mg. per 100 c.c. were found in six of the 16 periods of treatment. All six of the patients with an elevated urea obtained some relief of symptoms and five had toxic symptoms to warn the patient to stop taking vitamin D. However, one patient with a blood urea of 46 mg. per 100 c.c. had no symptoms to warn him of the toxicity of the vitamin D for the kidneys. By the time the concentration of urea was elevated, that of the serum calcium was also elevated. A normal concentration of blood urea was not an indication that the patients would experience symptomatic improvement or symptoms of toxicity. It is apparent that an elevated level of blood calcium is much more readily produced than is demonstrable damage to the kidneys. Large doses of vitamin D may produce damage to the kidneys sufficient to elevate the blood urea. In each case the concentration of urea returned to normal after administration of the vitamin D was discontinued.

SUMMARY

Large doses of vitamin D have been of help in partially controlling the symptoms of infectious arthritis in seven of 14 patients and in 68 per cent of 25 courses of treatment. Very little effect was seen on the objective

findings in the patients so treated. Vitamin D is not a specific agent for the control of infectious arthritis. Exacerbations may occur while the patient is taking large doses of vitamin D. The beneficial effects are only transitory, as a return of symptoms usually occurs after discontinuing its use. There is some risk of renal damage, which is apparently temporary if the administration of vitamin D is discontinued promptly after evidence of toxicity appears, but serious damage may occur. It is not necessary to produce toxic symptoms or renal damage to obtain clinical improvement.

There is no good correlation between clinical improvement and toxic symptoms or renal damage as evidenced by retention of urea. However, 11 patients who had an elevated concentration of blood calcium had clinical improvement and of four who had normal calcium, two experienced improvement and two did not.

Gastrointestinal upset was the most frequent sign of toxicity and usually gave adequate warning of the toxicity of the vitamin D; however, in one case the concentration of urea became elevated without the occurrence of any gastrointestinal upset. Patients receiving vitamin D should be watched carefully for symptoms of toxicity. Vitamin D therapy should be considered as one of many types of treatment which is sometimes of help in the temporary and partial control of symptoms of infectious arthritis. It is of very little, if any, use when lasting improvement is sought for the patient who has infectious arthritis.

The frequency of toxicity in this series is higher than has been reported in other series of patients treated with vitamin D. This may in part be due to other preparations being used by some of the other investigators.

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MENTAL SYMPTOMS FOLLOWING CARBON DISULPHIDE ABSORPTION AND INTOXICATION *

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The new therapeutic attack upon psychiatric conditions hitherto treated passively or empirically is a most encouraging development. The advent of new drugs and new methods, chemical, biological, and electrical, has changed the prognosis of mental disease and placed psychiatry in an enviable position, for it has progressed further in the past decade than many of its sister branches of medical science. As in all other branches of medicine, preventive measures play a most important part and the contributions of mental hygiene are of inestimable importance. We are beginning to recognize that there is a form of industrial mental hygiene the importance of which is as yet not completely appreciated. It merits our attention as this paper will demonstrate, and a careful survey of the mental health and mental hygiene measures in those industries with high morbidity rates would probably go far toward reducing the admissions to mental hospitals.

This paper is concerned with the results of the psychiatric examination of 120 workers employed in the viscose rayon industry. In the course of their daily work these individuals had been exposed to carbon disulphide fumes in varying intensity depending upon the department in which they were employed.

The occurrence of CS_2 poisoning and the opportunity for frequent contact with persons suffering from it are obviously small and limited to a few industrial centers. Despite the fact that exposure to carbon disulphide is a recognized industrial hazard, many experienced practitioners will never encounter its effects, and yet it cannot be said that a study of this kind is merely of academic importance. It reminds us of the necessity for questioning patients about their past and present occupation and of the importance of industrial hazards and occupational diseases. It would be most difficult to diagnose chronic CS_2 intoxication if the physician were not aware of the type of work his patient was doing.

Chemical Properties of CS_2

The disulphide or bisulphide of carbon is a colorless, transparent fluid of sweetish aromatic odor. When impure it smells like radishes. It boils

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The literature abstracted above was selected. A complete list of references is appended to Bulletin No. 46 of the Occupational Disease Prevention Division of the Department of Labor and Industry, Commonwealth of Pennsylvania. This bulletin is the report of a survey made by Dr. F. H. Lewey and a group of specialists from the University of Pennsylvania Medical School.

at 104.8° F. but volatilizes at room temperature. Mixed with air it is inflammable at 302° and if mixed with 20 parts by volume of atmospheric air it is highly explosive. Carbon disulphide shares this property with the group of gaseous anesthetics of which it is a member. Simpson, the famous Scottish surgeon who introduced chloroform into surgery and obstetrics, tested carbon disulphide as a narcotic years before it was used for any other purpose. Since Lewin's experiments in 1878 it has been recognized as a most severe neural poison probably because of its fat solvent properties. Its main avenue of entry into the body is through the lungs where it immediately permeates into the blood and is transported into the other organs including the brain. Its further course in the body is a matter of conjecture but we do know that 40 per cent of the carbon disulphide content of the blood disappears during the first hour after the worker leaves the poisonous atmosphere and 25 per cent additional during the second. It is eliminated in the urine and through the skin and lungs. The greatest part of the carbon disulphide inhaled is dissipated in the breath.

Historical Data and Literature

In France, in the middle of the last century a new industry was introduced which used the sap of a tropical tree. Its resin, known to the French as caoutchouc and to the English as "India Rubber" arrived in Europe in the form of hard balls and had to be softened before it could be spread on canvas for use as rubber sheets manufactured into such articles as toy balloons. Carbon disulphide (CS_2), concerning whose poisonous qualities nothing was yet known, proved to be the best rubber solvent. The new rubberized fabric was a great success and a lucrative new trade was established in the home workshops of Paris. Here, in small rooms usually combined with living quarters, parents and children worked from morning until night in an atmosphere saturated with carbon disulphide vapors. Heating was costly, so none of the warm air was allowed to escape through the windows and the necessity for ventilation as a health measure had not yet been conceived.

In 1856, August Delpech,[1] a "public health minded" physician of the famous Bicêtre Hospital in Paris, published a report of 24 cases of carbon disulphide poisoning in "L'Union Medical," and in 1863 the report was extended to include 80 more cases. Delpech completely covered the entire scope of carbon disulphide intoxication in the fields of neurology, psychiatry and internal medicine, its prognosis, its industrial and sociological aspects so that only details could be added by later publications. He also fully described the case of one Victor Delacroix, aet. 27, who in the course of his work was exposed to carbon disulphide fumes. He noted the extreme irritability and inexplicable rages evidenced by the patient, some of them leading to violence. He noted the sexual difficulties, the insomnia, bad dreams, and in fact described the whole toxic syndrome which we were to confirm independently 80 years later. As an interesting sidelight, he described the patient's son, a sweet-tempered lad who played in his father's

workshop, and who after three days' exposure to carbon disulphide gas became excited to the point of fury and attempted to attack and injure his father.

For nearly 20 years after the original paper, the French literature had a monopoly on the subject. In 1881 Tamassia [2] reported from Italy the results of animal experiments with carbon disulphide. In 1884 Alexander Bruce [3] described two typical cases of carbon disulphide intoxication from Edinburgh. In 1886 E. Mendel [4] aroused the interest of the medical profession in Germany by exposing the dangers of carbon disulphide in the "cold" vulcanizing process.

Unfortunately through some mischance, the work of the great Charcot [5] was responsible for beclouding the issue. In 1889 he presented a patient in his clinic whom he diagnosed as having "sulphide of carbon neurosis." The patient was hemiplegic, depressed and complained of terrifying dreams. Charcot stated that this was a form of hysteria but admitted that it was not the type which lends itself to hypnosis. He further stated that while some of the symptoms described by Delpech were probably due to carbon disulphide vapors, most of them were due to hysteria. His contemporary, Marie,[6] agreed with him and the bizarre findings were labeled hysteria. The opinions of these two masters threw other investigators off the track and remnants of their errors still remain in some places. Another controversial question arose, namely, is there such an entity as a true carbon disulphide psychosis or does the carbon disulphide merely act as a trigger which releases a latent psychosis in a predisposed individual? There was a great difference of opinion, due not so much to a contradiction of facts as to the differing basic conceptions of two antagonistic psychiatric schools.

Laudenheimer's [7] monograph stressed the importance of carbon disulphide as an exogenous poison which might initiate a psychosis. However, he went too far and included some incurable forms of dementia in his group and attributed them to carbon disulphide. Bonhoeffer [8] reported 14 cases of carbon disulphide psychosis, eight in rubber workers and six in viscose rayon workers. In the same report he examined critically Laudenheimer's cases and stated that five of them were typically toxic psychoses and the remainder were probably schizophrenic.

Laudenheimer's opponents went to the other extreme and ascribed to carbon disulphide the rôle of *agent provocateur* only. Today Bonhoeffer's thesis that there can be no doubt of the existence of a toxic psychosis due to carbon disulphide has won general acceptance and we hope to add further confirmation of it in this paper. In his monograph Bonhoeffer clearly defines the criteria by which a toxic psychosis can be diagnosed. He states that in toxic psychoses (which he calls amentia) the following characteristics can be noted. Early there is (1) clouded consciousness; (2) restlessness and very acute motor excitement; (3) hyperacuity of all senses, especially optic; and, (4) increased emotionalism. Secondarily, or as a consequence, there appears incoherence, perplexity and amnesia for the time of the psychosis.

Finally, there is an acute psychosis passing over into a chronic psychosis of the Korsakoff type. He felt that a diagnosis of toxic psychosis due to carbon disulphide intoxication should be made only on the basis of recovery after an illness which did not exceed several months or a year at most.

In America, Peterson [9] in 1892 described three cases of mania which occurred in individuals who worked in the same room of a rubber factory and were exposed to carbon disulphide. All three patients recovered. In the same year, 1892, Bard [10] reported two cases of acute mania in rubber workers. One patient killed a man whom he thought had wronged him and then destroyed himself. In 1904 and 1905 three cases of carbon disulphide intoxication in workers of "an artificial silk plant" were reported by Jump and Cruice,[11] and by Francine,[12] from the Hospital of the University of Pennsylvania. Francine's patient began to suffer almost from the first day of his employment. He slept poorly, lost his appetite and was exhilarated while in the factory and depressed when out of it. The night before he was taken to the hospital he had a peculiar attack during which he was confused, delirious and maniacal. This was most probably a case of acute carbon disulphide poisoning. The cases described by Jump and Cruice were examples of this chronic intoxication. One of them is described as being at first exhilarated and loquacious when he went to work in the churn room; later he became depressed, tactiturn, irritable, suffered from insomnia, memory defects and loss of sexual power.

Twenty years later, Dr. Alice Hamilton [13] listed in her book, "Industrial Poisons in the United States," the risks of carbon disulphide intoxication in viscose rayon plants. From Holland, Kranenburg [14] wrote on the subject in 1925; in 1928 Quarelli [15] reported that almost 33 per cent of the viscose rayon workers in Torino developed Parkinsonism. The situation in America remained unchanged, however, until Dr. Alice Hamilton again raised her warning voice in 1937.

In 1938 Gordy and Trumper [16] reported six cases which they had examined, three acute and three chronic, four women and two men. The symptom complex was practically the same as that noted by other workers. They state that one patient, a woman, had lilliputian and brobdignagian hallucinations and that this was the first time this had been chronicled in the literature. All of their cases were invalids.

Method of Examination and General Considerations

It should be noted that none of our patients was an invalid; they were all ambulatory and, with three exceptions, all were working.

The psychiatric examinations were conducted by means of informal talks and the use of simple memory tests. Where the patient's mental ability was in question efforts were made to determine his approximate status. Usually the examiner was fortified by means of a questionnaire which had been filled out previous to the examination and which facilitated the work considerably.

Particular attention was paid to the spontaneous remarks of the patient and the approach was changed frequently in order to avoid the possibility of a worker's being prepared for the examination by those who had already been interviewed. Fortunately, it was possible for the psychiatrist to interview one-fourth of the group within 15 to 20 minutes after leaving their respective work rooms.

In addition to the patients examined, the records of all of the mental hospitals in the surrounding areas were also carefully gone over and particular attention was paid to anyone who had been exposed to carbon disulphide.* This was a herculean task, but it proved to be very much worth while, and later we will speak of the convincing indications of toxic psychoses which were unearthed.

The Acute Psychoses

In the routine examinations, three workers were seen who were definitely mentally ill at the time of the examination. All three were employed and two of them had come directly from work to the examining room. One man, aged 38, was led in by a fellow employee. He had been working in a part of the plant where the exposure was greatest. On the night of the examination the foreman had noticed that something was wrong and had transferred him to another department in which both the work and exposure to the gas were light. The patient was confused and disoriented; he complained of being "in a fog." He said he knew something was wrong, he had been nervous and irritable for several months but the condition was much worse in the past few weeks. He appeared more like a man of 50 years than 38 which he claimed to be. He complained of extreme irritability and rapid mood changes. He was unable to control the overwhelming impulse to anger—at home or in his shop. He had been unable to sleep more than two hours at a time; when he did sleep, it was broken and troubled and he dreamed of falling from great heights, of robberies, etc. At times he was "flighty and sleepy" during working hours, but he was covered and protected by the other men so that he would not lose his job.

His memory had been poor for months. He would go into stores and forget what he went for. At the time of the examination he could not recall the day or date. He could not repeat four digits after one minute. Several times during the examination he forgot the topic of conversation. Peculiarly enough, his memory for past events was good. He felt that the transfer would facilitate his return to health. He believed this was the second time that the gas had "gotten him." On the previous occasion, following his transfer to another department he had improved within a week or two.

He complained of complete loss of libido after a period of gradual lessening. He had become seclusive because he was not fit to be in the

* Credit should be given to Miss Lillian Erskine, formerly consulting expert of the Department of Labor. Her indefatigable work resulted in the breaking out of all of these case histories.

company of others. He was sorry to be so angry and so wretched in his relationship with his family and fellow workmen.

The second patient presented the same type of picture with the addition of a definite hallucinosis of both the visual and auditory type. In addition to his psychotic findings the man had organic nervous signs and symptoms. In his hallucinations he could see the " spirit of a woman." He could also travel great distances and explore foreign lands with a realty which frightened him. He could listen to the song of birds at times when no one else could hear them. There was no evidence of dementia praecox nor were these hypnagogic hallucinations.

The third patient in question, a man of 42 years, showed more agitation than the others. He said his memory was so bad that he feared losing his mind. He was so irritable that he felt like killing his children and at times had actually threatened to do so. He was bothered by terrifying dreams which caused him to cry out and his wife would have to awaken him. He told his wife that time would tell what would happen to him—" whether the work would kill him or he would end in an asylum." He added that he had worked 16 years in another plant and nothing like this had occurred, that he had never even had an argument. He would " see things " at times and then would get scared when he realized they were hallucinations. There were also some vague paranoid ideas.

Five other patients who presented a severe toxic syndrome at the time of the examination gave evidence of previous psychotic episodes. Some of them had been confined in mental hospitals. One of the patients gave a history (which was later verified) of having upset the bed and thrown his wife on the floor, he urinated in the radiators, and became lost in his own house which contained only four rooms. He was furloughed from work and improved rapidly.

In evaluating the histories of the cases unearthed in the mental hospitals, we considered only those which were definite uncomplicated toxic psychoses in people who had been exposed to carbon disulphide at the onset of the illness. Many of them were taken ill while at work. One complicating factor occurred often; the patients' reactions were usually of the manic type and as a result, they would become loud, aggressive and combative; the general hospital was not equipped to handle them so they would be arrested and taken to the local jail. It usually took about three days to complete formalities for admission to the state mental hospital and on several occasions, the patients cleared up shortly after their arrival in the institution.

The following brief summary of one case exemplifies others which were selected as definite carbon disulphide psychoses.

Case 13. Male, aged 33, married. He was exposed to carbon disulphide for two months and eight days. No familial history of mental or nervous disease. He was taken acutely ill while at work and was admitted to the hospital handcuffed, maniacal, violent, assaultive, hallucinated. His symptoms cleared up shortly after admission to the hospital. Physically, his condition was good. The heart and lungs were

normal. The pulse was 90 and the systolic blood pressure 120, diastolic 80. Other systemic examinations were negative. The pupils were dilated. The patellar reflexes were unequal—more active on the left side. The Babinski sign was absent. There was a fibrillary tremor of the tongue and slight tremor of the hands. The Wassermann reaction was negative. The urine showed traces of albumin and sugar. He recovered quickly and thoroughly except for amnesia; the entire experience was lost and not regained. He was paroled after several months and remained symptom free. Immediately prior to his illness his wife had noticed that he was acting queerly—"voices began" and he "went around and around." He also showed the brobdignagian hallucinations mentioned by Gordy and Trumper in that he "felt taller than everyone."

This case is typical of the others except that recovery was more rapid. The other nine patients discovered in mental hospitals recovered, in from two to four months, the longest taking six months and 21 days. It is a notable fact that even though the patients became entirely clear mentally their memories remained poor.

The following brief table gives a summary of the cases found in mental hospitals.

TABLE I

	Age	Sex	Length of Exposure to CS_2	Onset	Symptoms	Duration
Case 1	33	M	2 mo., 8 days	Acute	Violent, assaultive, hallucinated, delusional	3 days
Case 2	62	M	12 years	Acute	Resistive, assaultive, confused, grandiose	4 mo., 10 days
Case 3	24	F	7 years	Over 2 weeks	Hallucinated, maniacal, overactive, overtalkative, rapid mood change	6 mo., 21 days
Case 4	23	F	3 years	Acute	Confused, violent, profane, rambling, delusional	10 days
Case 5	27	M	5 weeks	Acute	Grandiose, excited, talkative, hallucinated	3½ mos.
Case 6	30	M	Unknown	Acute	Violent, noisy, destructive, confused, delusional	Died of intercurrent infection
Case 7	39	M	5 years	Acute	Visual and auditory hallucinations, combative, delusional, suspicious	8 weeks
Case 8	50	M	3 years	Acute	Neurological signs, vomiting, giddiness, extreme nervousness	2½ years
Case 9	45	M	Unknown	Acute	Delusional, hallucinated, overactive, amnesia	4 months (relapsed later)
Case 10	53	M	Unknown	Gradual	Combative, depressed, delusional, amnesia	4 mo., 4 days

Usually the psychoses resulting from exposure to carbon disulphide are of the manic type with acute confusion, delirium and hallucinations. The onset is generally acute but in many instances there is a gradual personality change manifesting itself to members of the patient's family or his friends

and fellow workmen. It is an insidious change and is noticed after varying periods of exposure to the gas. There is a phase of irritability accompanied by headache and insomnia and also a period of depression. The libido is markedly lessened or disappears entirely. Dreams of a terrifying nature frighten the patient and constant repetition of them, night after night, makes him reluctant to attempt to secure the meagre sleep which he needs so badly. The patients frequently become seclusive. The actual break may come while the patient is at work. An English report states that in one instance it was necessary to board up the windows of a factory to prevent maniacal patients from jumping out.

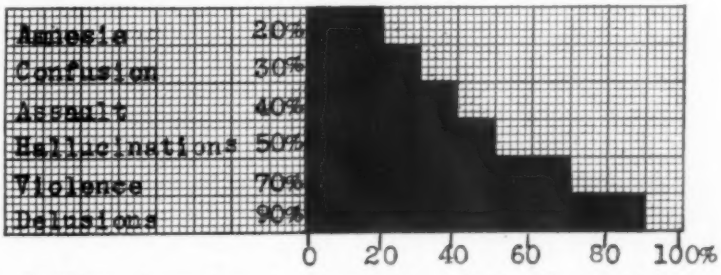

FIG. 1. Incidence of symptoms in 10 psychotic patients. Expressed in per cent.

Rodenacker was of the opinion that carbon disulphide has a special affinity for individuals of the cyclothymic type. He also suggested that carbon disulphide psychosis was not per se a toxic psychosis but rather that it was an intoxication occurring during a maniacal or depressive phase. We are unable to subscribe to his theory. Our studies indicate that there is a carbon disulphide psychosis, that it is a definite clinical entity and it is of the toxic type. Rodenacker goes further and states that he believes the schizoid type of individual to be comparatively insensitive to carbon disulphide and describes one man of this type who felt well while exposed to carbon disulphide fumes in concentrations which caused discomfort to his fellow workmen. However, we saw several individuals of asthenic habitus and definite schizoid make-up who were adversely affected by the fumes. True enough, some of the patients felt better while in the carbon disulphide atmosphere but this was early in their exposure and it had no relationship to their body build.

The rôle of carbon disulphide as an "agent provocateur" will be considered at a later time. We have examined several patients in state hospitals who were diagnosed paranoid schizophrenia. One man was of particular interest. He had had a previous mental break years before while exposed to high concentrations of carbon disulphide. He recovered, was able to carry on his work and did very well until he was returned to the same department and the same high carbon disulphide concentration in which he became ill before. We are aware of the psychological hazard to the patient upon being returned to the department in which he and other workers had

become ill. We also examined the records of other patients who had presented schizoid symptoms, and while we believe that carbon disulphide was the exciting cause of the attack, we are as yet unable to prove this statement.

Altogether, we rejected 20 suspicious cases because of some complicating factor. In five instances we felt that the data were insufficient. Seven cases were discarded because of specific serologic findings. One man had evidences of cerebral arteriosclerosis at the age of fifty. One had a manic depressive history and three were schizoid personalities. Three were discarded because the duration of the illness seemed too long for a carbon disulphide psychosis.

Chronic Absorption and Intoxication

In order to facilitate the report we have divided the record of the non-psychotic patients into four groups. They are designated by number and will be described later. To avoid confusion of symptoms we completely rejected five workers because they had extraneous complications. One of these had sustained a skull fracture in an automobile accident, two were chronic alcoholics, one had syphilis and one patient was 69 years of age. It was thought wiser to reject these men than to try to separate out the symptoms. Peculiarly enough, all five of the patients would have been classed under our mildest group. The remaining workers are designated as follows:

Group 0—Negative, no evidence of toxic symptoms.
" 1—Mildly affected.
Group 2—Moderately affected.
" 3—Severely affected—toxic reaction.

The negative group consisted of 14 workers. They are regarded as negative from a psychiatric standpoint. Their ages ranged from 28 to 53 years. The shortest term of exposure was five and one-half years and the longest term 26 years. Even though these patients had no definite symptoms they all complained of increased irritability. Only two of the group had worked in the sections which were exposed to the gas in high concentrations. One of the men who had worked in a mild exposure of carbon disulphide for 25 years was negative from a psychiatric standpoint but he presented some organic neurologic signs.

Group 1 (Mildly Affected). There were 32 workers placed in this group. The standards by which they were judged could not be rigidly defined. The presence of one or several symptoms of toxicity in a mild form qualified the patients for admission to this group. While many of the complaints were apparently mild at the time of examination, they did not augur well for the future. One worker complained that he " got burnt up " very quickly and that he had engaged in numerous quarrels. This is seemingly not very serious but this patient was perplexed by his conduct, he had never acted this way before. He was afraid that if it had continued he

would have killed a man. He was laid off from work and after he had been out for one week, his disposition improved, he became more gentle and friendly and got along better with his family than he had for years. Another worker, in this same group, had been formerly nicknamed "Happy"; at the time of his examination he stated that this was a sad misnomer, he was depressed because of his irritability and quarrelsomeness. The same man complained of terrifying dreams of snakes and horrible things such as robberies and "killings." He stated that at times when he retired his body would seem so light that it would float away from him. He would have at times—"a dream within a dream," i.e. he knew he was dreaming and hoped his wife would awaken him as he was powerless to help himself.

In two of the cases examined in this group the workers were believed to be low grade morons and not too much significance was attached to their subjective complaints.

The following examples are typical of this group.

Case 1. Male, aged 25. He had been employed for four and three-quarters years. The change of personality had been noted by others as he had become restless, easily excitable, and irritable. He would get a "funny leery feeling," was apathetic and easily fatigued. He slept little and poorly. During sleep he had sensations of falling. He had beginning paranoid ideas about fellow workers. He would get sick after being off for two days, but as soon as he got back into the fumes he felt better. His libido was diminished. He has since been laid off for two months and gained 20 pounds. Once before when out on strike for nine months he gained 40 pounds. He also has other medical complaints.

Case 2. Male, aged 31. There had been heavy exposure for approximately four years. He felt that he was a nervous man, being fidgety—and restless. His sleep was interrupted; sometimes for weeks at a time he would get very little sleep at all. He was not worried about anything but would simply lie awake and think about irrelevant things. He dreamt about things which frightened him, and jerked in his sleep. He frequently became depressed and was at a loss to understand why, because "things were running smoothly enough." His memory had been fairly good but if he got excited he became confused. His "mind wandered" more than it did before.

Group 2 (Moderately Affected). Twenty-five patients were placed in this group. The symptoms presented here are more pronounced but are still not serious enough to be considered a definite "toxic reaction." Sixty-four per cent of these patients complained of memory defect about which more will be said later on. Only two of the 25 patients were churn room workers (supposedly the location of the greatest carbon disulphide exposure) while the remainder were spinners and workers at miscellaneous jobs. Typical cases of this group follow.

Case 3. Patient, 32 years old, male. Exposure was moderate. He had four children, and had been 11 years with present company. He had been getting increasingly irritable and angry for about the last six years. "Things get on his nerves." He tosses about all night in his attempts to sleep and sleeps one hour at a time. He has bad dreams occasionally. He was sick and was off duty for four weeks and at the end of this time he felt well. Once he had ten days' vacation and on the sixth day felt perfectly well. He states that the "fumes don't agree with him." His memory

used to be good but it is poor now. He loses and forgets things. He was formerly interested in his home. Now he has lost interest and just does nothing. His libido has become markedly decreased. He believes that if he could just get one good night's sleep, he would feel much better.

Case 4. Male, aged 37. Mild exposure during 16 years' employment by a viscose company. He complains that he is irritable and mean with his wife and children. Formerly he had real hard work with another company but was never like this. He rolls and tosses all night. He sleeps 15 minutes and thinks it has been eight hours. He has frightful dreams, gets scared and gets up to examine the doors and windows. At times he has gotten up out of bed and called out of the window, was afraid someone was after him. There is a marked change in his personality. His memory has noticeably "gone bad." He goes to night school—takes courses and tries to advance himself, but it seems to be impossible. His libido has been lessening for the last seven years. The last two years it has been especially bad. Marital relationship is no longer pleasurable—it is a task. He has neither the desire nor ability to accomplish sexual relationships. He was formerly interested in an avocation but he has now given it up because of apathy.

Group 3. The Toxic Reaction (Severely Affected). This group includes twenty-one workers. All gave evidence of a toxic process and all of them had been exposed to varying concentrations of carbon disulphide. They were recruited from two factories widely separated and in both places insufficient attention had been paid to industrial hygiene and preventive measures. At this point we should again call attention to the fact that the patients presented many additional symptoms, referable to all other bodily symptoms but in this paper we are simply reviewing those which come under the domain of psychiatry. Several examples of this group have been abstracted and presented below.

Case 5. Male, aged 36. He is prematurely aged and gives the appearance of 55. He has been at this type of work for 10 years and has been under heavy exposure for last three years. He is more irritable than ever before and is worse at night ("You can go back over my record at home; I was formerly easy going—now I can't take it; I am ready to fight everybody"). His wife says he is losing his mind—"is forever angry and arguing." He can hardly get himself to sleep. He awakens after one hour and thinks the whole night has passed. He jerks so badly that children had to be removed from the bedroom in his small house. His dreams are bad, of fights, killings, etc. He fights and groans and gets scared. His memory is bad. "If you send me to the postoffice, I might get there and might not. I used to have a good memory, can remember things in my boyhood but almost forget this morning." His interest is narrowing and he has no energy. He gets as tired as a man of seventy. His libido is gone, the change beginning months ago. He hears "people hollering" and when he looks there is no one there. He has optical illusions while at work and these illusions are concerned with the churns. "I was never a nervous man before. I never took a pill till nine months ago—since then I have taken enough to kill all the people around town."

Case 6. Male, aged 34. Although exposed for 13 years, he feels that he was mild tempered up until one year ago. Now he is so irritable and angry at home that his wife says he is one of the meanest men who ever lived. He is ashamed and worried about this. He is terribly fatigued upon retiring but after three hours' sleep bounds out of bed fully awake. He does not understand this. He has many bad dreams, about fire, falling, running away, etc. He is now very much afraid because

recently he was so angry that he wanted to kill his wife. This scared him and he wants to do something about it. The two years he was out of the plant he felt like a normal person. He fears running into things as he walks. He has seen horrible, grotesque faces and he was so frightened that he said his prayers! With his eyes open or shut he saw these faces. His libido is markedly lessened. When he attempts intercourse (infrequently) he fails miserably.

It was apparent from analysis of this group that a definite toxic syndrome presented itself. It consisted of the following symptoms which were fairly constant. (1) Personality change (always for the worse); (2) marked irritability; (3) memory defect; (4) insomnia; (5) bad dreams; (6) lessening of libido; and (7) constant fatigue.

TABLE II

Percentage of Incidence of Psychic Symptoms in 78 Viscose Rayon Workers, Subdivided into Three Groups of Severity

Grade of Severity	Actual Number of Members in each Group	Change of Personality	Memory Defect	Marked Irritability	Lessening of Libido*	Insomnia	Bad Dreams	Marked Fatigue†	Hallucinations	Delusions	Depression	Confusion
I	(32)	40.5	31.5	43.6	43.6 1)	40.5	37.5	31.5 2)	4.1	0	0	0
II	(25)	52.	64.	56.	36.	44.	44.	12.	12.	4	8	8
III	(21)	90.1	86.	81.	66.8	62.	57.	47.5	23.8	23.8	23.8	14.3
I–III r.	(78)	58. +0.97	56.5 +0.96	58. +0.98	47.5 +0.72	47.5 +0.93	45. +0.98	29.5	11.6 +0.995	7.7	9.	6.4

* The comparatively smaller number of workers in this group may be caused by the fact that in order to avoid error, men over 40 years of age were not considered; this increased the sampling error.

† Another sampling error was detected. In one group the question about fatigue was omitted.

Table 2 indicates that the frequency of psychic symptoms increased with the severity of carbon disulphide absorption. This is confirmed by the correlation coefficient (r) strongly suggesting an upward trend in all columns. Statistical significance cannot be attached to only one column: hallucinations; $r = 0.995$, $P = 0.06$.

The average number of psychic symptoms amounted to 2.7 in Group 1, to 3.3 in Group 2, and 5.8 in Group 3.

TABLE III

Percentage in Which Churn Room Workers, Spinners and Workers in Miscellaneous Viscose Departments Shared in the Three Groups of Severity

Groups of Severity	I	II	III
Churn Room	31.2	8.	57.
Spinning Room	59.4	72.	38.2
Miscellaneous Rooms	9.4	20.	4.8

The group of the spinning room workers contributed more than one-half to the mild cases and almost three-fourths to the moderately severe cases but only somewhat over one-third to the severe cases. The churn room workers, correspondingly, represented not fully one-third of the mild cases but over one-half of the severe ones. One-fifth of the members of Group 2 consisted of workers of odd jobs such as pipe fitters, filter press cleaners and engineers who are sometimes very much exposed to fumes.

The Individual Symptoms

Regarding the irritability and anger little more can be said. They were recognized by the workers' family and colleagues and regarded seriously. During these phases the patient was left severely alone. The outbreaks of anger are usually short lived and are followed by a feeling of abject penitence during which time the patient frequently cries and complains that he is powerless to help himself. At times the rage assumes serious proportions and we noted several instances in which they were contributing factors toward broken homes. A general practitioner who was in no way connected with this survey informed us that the conduct of the people who lived in houses close to the mill, which were permeated by odors from it, was of an entirely different type from that of those who lived out in the country. He had observed them for several years and he felt that their conduct was characterized by lack of inhibition. Quarrels were frequent and marital difficulties marked. It can be noted that some of the earlier writers felt that lack of inhibition was one of the most frequent early signs of carbon disulphide intoxication.

Regarding the memory defects, when the subject was introduced it frequently brought immediate and emphatic response. Usually it was introduced by the worker himself. This was the more remarkable when it is remembered that many of the workers had not yet attained their fortieth year. It seems as though the memory loss was particularly for recent events, although this will have to be substantiated by further examination. Coupled with a progressive narrowing of interest and some arteriosclerosis plus the premature appearance of age in a portion of this group, it requires further study. Some of the spontaneous remarks about memory defects would have been amusing had they not been pathetic. One man had forgotten where he parked his car and was forced to wander about in a small town looking for it. A complicating factor was that his wife was in it. (We are aware of the possible analytical significance of this.) Another man had to be removed from the churn room because he could not remember the time of the charges. When some of the men were sent to the store for more than two items it was necessary to write them down. Several remarked significantly that if they were sent out for three things they would be bound to forget one of them. The constant complaint of loss of memory for names was disregarded because of its universality, but findings such as the one which follows cannot be disregarded. One man being questioned about his memory remarked, " Memory. You have me there. It started to go back on me on my first time in heavy exposure to the gas. I have to ask my wife what day it is. I used to have a good memory—I was noted for it, but no more." This patient failed to memorize three written digits in a period of three to five minutes as did four other patients. Approximate dates of illnesses, vacations, strikes, etc., which would ordinarily be retained were lost to some of the men. Some remarked that when they were off from work for a long period of time their memories improved.

A large percentage of the men complained of sleep disturbances. These were frequently difficult to evaluate because they were on "shift work" and those who had worked at night would have difficulty in sleeping during the day. This particular complaint is not confined to these workers and might be found in other men who worked on night shifts. Even allowing for this, however, there were definite changes in the sleep rhythm. Almost without exception the men complained of excessive fatigue and yet their sleep was broken and meagre. The two exceptions to this complained of a constant overwhelming desire to sleep and one had to be awakened during his meals. One curious fact was noted. Most of the men stated that if they fell asleep for 15 or 30 minutes they would awaken feeling as if they had slept five or six hours, without being refreshed. Two phenomena contributed to the broken sleep; one was "jerking" and the other was bad dreams. The first mentioned varied in intensity and some only became aware of it because their wives had so informed them. Others complained that the jerks were so marked and so sudden that they were awakened by them and the most severe cases were at times almost jolted out of bed. No one of the 110 men examined had dreamt of pleasant things. Some few did not dream at all and the remainder dreamt either of work or of horrible things. Mostly they were concerned with murders, suicides, falling from high places and fights. One man on the night before the examination dreamt that someone had pulled all of his teeth out. These observations agree in substance with the findings of other writers.

Some authors have stated that in carbon disulphide intoxication the libido is increased at first and only after continued exposure does it become lessened. While we searchingly questioned all of the workers we were unable sharply to demarcate these periods and men who had been exposed for a number of years stoutly denied interference with this function while others whose tenure was relatively short were apparently greatly affected. This recalls the two cases reported by James Ross in whom sexual function was lost after three weeks' exposure to the fumes. In two of our cases this change contributed to the separation of man and wife, while one man still in his twenties complained that because of his loss his wife had accused him of infidelity. In order to obviate any possibility of the age factor complicating our statistics we set 40 years as the arbitrary figure above which we would not consider loss of sexual power unusual; this figure is eminently fair and far below the normal age level for loss of libido.

It is impossible to explain the symptoms listed above as evidences of mass hysteria. True enough, there are instances of hysteria being found among these workers the same as in any large group. Our findings corroborate the findings of other investigators in foreign lands. Many of the men who have been mentioned here also had other measurable physical signs. As the final and deciding factor, the results of our animal experimentation leave no room for doubt; they are conclusive. These results have already been published.[17]

Conclusions

1. Acute carbon disulphide intoxication is comparable to the narcotic effects of other gaseous anesthetics.

Chronic carbon disulphide absorption is associated with the physical changes described by Lewey and attributed to liver damage and subsequent vitamin B deficiency.

2. Our survey convinces us that there can be no doubt of the existence of a toxic psychosis due to carbon disulphide.

3. In the carbon disulphide psychoses the following characteristics were noted: confusion, combativeness, hallucinations, delusions, depression, and finally, amnesia for the acute attack.

4. While the onset of the psychosis is usually acute, a gradual personality change has also been noted by attentive observers. This change is insidious and is accompanied by a phase of irritability, depression, headache and insomnia. The libido is lessened, and dreams of a terrifying nature occur. The break frequently comes while the patient is at work.

5. It is probable that carbon disulphide also acts as an *agent provocateur* in individuals who are already predisposed to mental illness.

6. A larger group of workers display a chronic form of absorption and intoxication symptoms. Apparently these symptoms are not dependent upon physical habitus or heavy exposure to the gas but rather to individual susceptibility to carbon disulphide.

7. The toxic syndrome consists of the following symptoms which are fairly constant: Personality changes (always for the worse), marked irritability, memory defect, insomnia, bad dreams, lessening of libido and constant fatigue.

8. It is apparent that once an individual has shown evidence of any toxic symptoms he should be removed from further exposure to carbon disulphide and never again be subjected to it in large quantities or in heavy concentrations.

9. It is essential that a vitamin rich diet be procurable in the cafeterias and homes of the workers in carbon disulphide.

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SULFANILAMIDE IN THE TREATMENT OF ERYSIPELAS *

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Prior to the use of sulfanilamide in the treatment of erysipelas, there was no effective mode of therapy. Early in 1935 Myer-Heine and Huguenin [1] treated 150 cases with the dye sulphamido-chrysoidin, reporting rapid and constant results as regard temperature and local phenomena. Kramer [2] in April 1936 reported 32 cases treated with prontosil, and expressed the opinion that it was the most effective drug used against the disease. Breen and Taylor [3] in June 1937 reported a series of 46 consecutive cases treated with prontosil in which the temperature fell to normal or below in 48 hours, and no spread or relapse occurred in any patient while taking the drug. Snodgrass, Anderson, et al.[4, 5, 6] conclude from a series of cases that sulfanilamide showed much better results than ultraviolet therapy in respect to the curtailment of the duration of the spread of the local lesion, of toxemia, and of the primary pyrexia. In a special report from the Herman Kiefer Hospital, in Detroit, in September 1938, Top and Young [7] compare an equal number of cases, 80 in each series, treated with anti-sera and sulfanilamide and conclude that anti-sera are of no material aid in the treatment of erysipelas. With sulfanilamide the temperature fell to normal within two days as compared to six and one half days with anti-sera, and the proportion of sulfanilamide cases which showed no spread was double that observed with serum treatment. The average hospital stay with sulfanilamide treatment was seven days compared to 14 days in serum treated cases. Nelson, Rinzler, and Kelsey [8] at the Bellevue Hospital treated 344 patients with sulfanilamide from January to July 1937, reporting an average of 6.8 days for the hospital stay. Hoyne, Wolfe, and Prim [9] at the Cook County Hospital reported on the treatment of 998 erysipelas patients from 1934 to 1938. Eight hundred and twenty cases were treated with various remedies with a mortality of 11.4 per cent as compared with 168 cases treated with sulfanilamide with a mortality of 2.46 per cent. The authors conclude that sulfanilamide is the most effective form of therapy thus far used in the treatment of erysipelas.

Beginning April 1937, all patients with erysipelas entering the communicable disease unit of the Los Angeles County Hospital were treated with sulfanilamide. From April 1, 1937 to August 1, 1939, 303 patients with erysipelas were treated. The average number of days of illness before admission was 2.6 days. The precipitating factor was determined in 37 per cent of the cases as listed in table 1; trauma, furuncles, and ulcers were the most common. Seventy per cent of the cases occurred between the months

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TABLE I

Erysipelas Showing Incidence of Precipitating Factors in 303 Cases

Precipitating Factors	Cases	Per Cent
Unknown	193	63.7
Trauma	30	9.9
Furuncle	20	6.6
Ulcers	15	4.9
Abrasions	7	2.3
Impetigo	6	1.9
Burns	5	1.6
Lacerations	4	1.3
Amputations	3	.9
Otitis media	3	.9
Mastoidectomy	3	.9
Miscellaneous	14	4.6
Totals	303	100

of October and March. The age incidence in table 2 shows that 11 cases occurred under one year of age, 20 cases between the ages of 1 and 4 years, and 39 cases after the age of 65 years. The sex distribution for all age groups was approximately equal. Sixteen per cent of the cases had one or more previous attacks. Graph 1 shows the distribution of areas involved;

TABLE II

Erysipelas Showing Incidence and Mortality Rates by Age Groups

Age Groups in Years	Males			Females			Totals		
	Cases	Deaths	Fatality Rate Per Cent	Cases	Deaths	Fatality Rate Per Cent	Cases	Deaths	Fatality Rate Per Cent
Under 6 Mon.	3	1	33.3	3	0	0	6	1	16.6
6 Mon.–1 Yr.	1	0	0	4	0	0	5	0	0
1	3	0	0	7	0	0	10	0	0
2	2	0	0	4	0	0	6	0	0
3	2	0	0	2	0	0	4	0	0
4	1	0	0	2	0	0	3	0	0
5–9	3	0	0	6	0	0	9	0	0
10–14	4	0	0	1	0	0	5	0	0
15–19	4	0	0	4	0	0	8	0	0
20–24	3	0	0	5	0	0	8	0	0
25–29	13	0	0	5	0	0	18	0	0
30–34	8	0	0	12	0	0	20	0	0
35–39	7	0	0	12	1	18.3	19	1	5.3
40–44	13	0	0	11	0	0	24	0	0
45–49	19	0	0	13	0	0	32	0	0
50–54	11	2	18.2	10	0	0	21	2	9.5
55–59	17	0	0	22	0	0	39	0	0
60–64	14	0	0	13	0	0	27	0	0
65–69	11	0	0	8	0	0	19	0	0
70–74	4	0	0	5	0	0	9	0	0
75–79	2	0	0	1	0	0	3	0	0
80+	4	0	0	4	0	0	8	0	0
Totals	149	3	2.0	154	1	0.66	303	4	1.3

51 per cent were of the facial variety, 30 per cent occurred in the lower extremities, and 19 per cent were elsewhere. The severity of the illness was classified according to the initial temperature on admission. Thirty-nine and six-tenths per cent of the cases with a temperature up to 101° were considered mild; 39.2 per cent of the cases with a temperature from 101 to 103° F. were moderately ill; 20.4 per cent of the cases with a temperature between 103 and 105° were severely ill; and 0.8 per cent of the cases had a temperature over 105°. One hundred and fifty-three cases had one or more associated diseases on admission as listed in table 3. Two hundred and

TABLE III

Erysipelas Showing Associated Conditions Present in 153 Patients on Admission

Associated Condition	Cases	Percentage Distribution of Totals
Hypertension Ateriosclerotic Heart Disease	46	15.1
Infections of the Upper Respiratory Tract	38	12.5
Syphilis	22	7.3
Carcinoma	11	3.6
Varicose Ulcers Legs	9	2.8
Chronic Alcoholism	7	2.3
Diabetes	6	1.9
Pulmonary Tuberculosis	4	1.3
Miscellaneous Conditions	77	25.4

forty cases had white blood counts on admission, the average being 12,350 with 70 per cent polymorphonuclears.

In the treatment of erysipelas with sulfanilamide the dosage was calculated as follows: For children up to five years of age, one grain per pound of body weight for 24 hours was given. One half of the total dose was given at once and the other half was given in divided doses every four hours over the remaining 24 hours. The tablets were crushed and given in food or drink. If the drug could not be given by mouth because of vomiting or the condition of the patient, it was given subcutaneously in a 1 per cent solution in normal saline every six hours. When the drug was given by mouth, steps were taken to prevent acidosis. When given by hypodermoclysis in the 1 per cent solution, 10 c.c. of ⅙ molar solution sodium lactate were added to each 100 c.c. sulfanilamide solution.* After 24 hours, the calculated dos-

* In 1937 the hospital laboratory carried out some experiments to determine whether or not sulfanilamide would remain stable when autoclaved. Since that time we have autoclaved all our sulfanilamide solutions for 20 minutes at 15 pounds pressure. We usually make up 100 liters at a time in single liter bottles, dissolving the drug in normal saline solution to which has been added sufficient sodium lactate to represent 100 c.c. of a ⅙ M solution (of sodium lactate) in each liter. We have observed solutions made in this fashion for as long as 12 months, and find that they remain stable and unchanged. However, at room temperature some of the drug will crystallize out over long periods of time. This is effectively overcome by setting the flasks in hot water until it redissolves. We have also used 50 c.c. of either lactated Ringer's solution or Hartman's solution per liter in place of sodium lactate. The sulfanilamide may be made up in an 8/10 per cent solution, and if a pure grade of drug be used, this will not precipitate out at ordinary temperatures. We see

age for the previous 24 hours was reduced one-third, and on the third day an additional reduction to one-half of the initial dosage was made. This maintenance dosage was given for three to five days after clinical cure to prevent relapse. In older children and adults the plan of treatment was

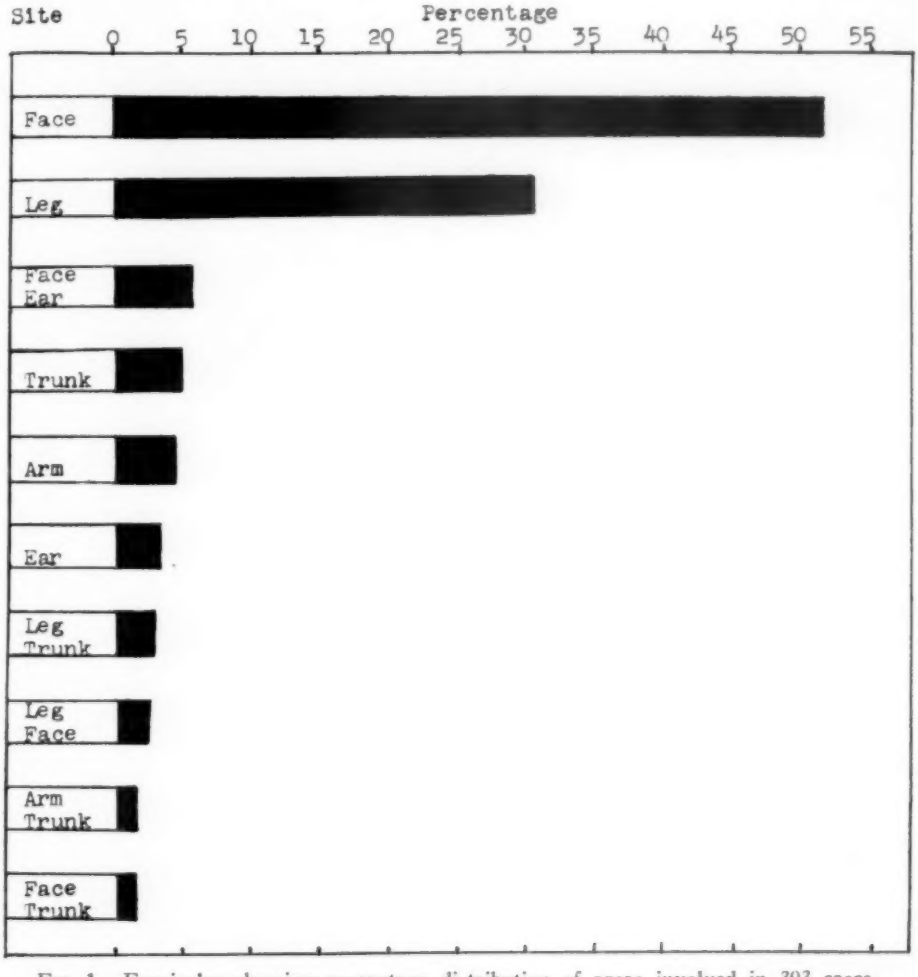

FIG. 1. Erysipelas showing percentage distribution of areas involved in 303 cases.

similar to that used in the younger age group, except the dosage was calculated at 15 grains for 20 pounds of body weight for 24 hours.

no particular advantage in the use of this latter solution, however, preferring to use the 1 per cent, because of the ease with which one can calculate the total amount of the drug given.

We have recently treated a number of cases of erysipelas with continuous wet compresses of a saturated solution of sulfanilamide and in a few other cases applied 2 per cent sulfanilamide ointment with gratifying results. The lesions regressed within 24 to 48 hours, although it was necessary to add oral sulfanilamide in some cases that did not respond adequately to local therapy. Traces of sulfanilamide were found in blood determinations following local treatment. The results indicate that local applications are of definite curative value; if, however, the lesions are extensive, oral sulfanilamide in addition is indicated.

Determinations of the sulfanilamide level in the blood were done in 121 cases. Ninety-four per cent of the determinations were taken 48 hours or more after admission. The average for the series was 5.8 mg. per 100 c.c.

TABLE IV

Erysipelas Showing Relationship of Sulfanilamide Level to Duration of Fever in 121 Cases

Number of Hours Elapsed between Admission and Blood Specimens	Number of Specimens Taken	Average Blood Level in mg./100 c.c.	Number of Patients Whose Temperature Became Normal at Period Noted		No Effect on Temperature	
			Number Cases	Per Cent Dist.	Number Cases	Per Cent Dist.
6	2	3.5	0	0	2	100
12	2	4.3	0	0	2	100
18	4	5.0	0	0	4	100
24	13	4.5	4	31	9	69
48	43	5.5	22	51	21	49
72	40	6.3	24	60	16	40
72+	66	6.6	62	95	4	5
Totals	170	5.8	112	64	58	36

Table 4 shows the relation of the blood level to the duration of fever. The only conclusion we could draw from our series was that the concentration of the drug in the blood in this disease need not necessarily be high to be effective.

TABLE V

Erysipelas Showing Results in 303 Cases Treated with Sulfanilamide

Age Groups in Years	Average Hospital Period in Days	Average Duration in Hours of Fever	Average Period in Hours Required for Lesions to Regress
Under 6 Months	8	48	62
6 Mos.–1 Yr.	11	52	48
1	12	50	43
2	7	52	38
3	6	32	48
4	5	44	51
5–9	9	63	45
10–14	6	27	34
15–19	8	38	83
20–24	8	74	58
25–29	4	31	46
30–34	7	71	45
35–39	8	47	57
40–44	8	54	51
45–49	7	50	56
50–54	6	36	45
55–59	7	48	47
60–64	7	33	50
65–69	8	44	51
70–74	9	57	46
75–79	7	60	48
80+	10	38	48
General Average	8	48	50

In table 5 are shown the results of sulfanilamide therapy in erysipelas: The average period of hospitalization was eight days for all patients treated, and was approximately the same for all age groups with the exception of the ages between six months to one year in which it was 11 days, and the age group between one to two years in which it was 12 days. The average time required for the temperature to reach normal was 48 hours for all groups of patients treated except in the age group between 20 and 24 years in which it was 74 hours, and in the age group between 30 and 34 in which it was 71 hours. In 71.4 per cent of the cases the temperature dropped to normal in 72 hours. The average time required for the lesion to regress was 50 hours for all patients treated, and this was approximately the average for all age groups except in the age group between 15 and 19 years in which it was 83 hours. There was no spread of the lesion in any case, and only one case in the entire series had a recurrence of the lesion.

Complications of erysipelas were as follows: Abscess formation, eight cases; pneumonia with hemolytic staphylococcus septicemia and lung abscess, one case; and nephritis with uremia, one case. The total complication rate was 0.3 per cent.

Toxic reactions attributable to the drug were as follows: marked cyanosis in 11 cases; marked nausea and vomiting in nine cases; in five cases, rashes which cleared up promptly when the drug was discontinued; temporary psychosis in five cases, in three of which it subsided when the dosage of the drug was reduced, and in two patients, only when the drug was discontinued; severe secondary anemias in two cases, which cleared up with discontinuation of the drug and institution of iron therapy; hemolytic anemia in two cases, 72 hours and 96 hours after treatment was started, both of which proved fatal; toxic hepatitis and nephritis in one case on the fifth day of treatment, which responded to treatment consisting of a blood transfusion and intravenous glucose.

Prior to the use of sulfanilamide in the treatment of erysipelas the mortality remained very high with the various methods of therapy. Dr. L. E. Sloan [10] reviewed 882 cases of erysipelas treated with various remedies at the Los Angeles County Hospital from 1929 to 1933 and found a mortality rate of 32.9 per cent in infants under one year of age, and an average mortality of 8.1 per cent. This mortality rate was approximately the same as those reported in large series of cases by other authors.[11] There were four deaths in this series, as seen in table 2, or a gross mortality rate of 1.3 per cent. One occurred in a male infant, 21 days old, as a toxic effect of the drug, an acute hemolytic anemia developing on the fourth day of treatment. The usual treatment with blood transfusions was used without avail. One patient, a female aged 37, developed a hemolytic staphylococcus septicemia while under treatment, with resultant lung abscess, which was proved at autopsy. One patient, a male aged 53, developed toxic nephritis with uremia on the third day of treatment. One patient, a male aged 54, developed acute

hemolytic anemia on the third day of treatment. The drug was immediately discontinued and three blood transfusions of 500 c.c. citrated blood were given without avail. Although the number of deaths was few, it is interesting to note that three were in males. Two deaths were definitely due to reactions from the drug, and the death from toxic nephritis with uremia may well have been due to a reaction from the drug. In spite of the fact that two and possibly three out of four deaths in this series were due to the drug, we feel that the results of its use have so consistently reduced the morbidity and mortality of erysipelas in all age groups, that its merits far exceed its dangers. We wish to stress the importance of careful observation and daily blood counts on all patients while receiving the drug.

In summary:

1. The literature on the treatment of erysipelas with sulfanilamide has been reviewed, showing excellent results from its use in this disease.

2. A series of 303 cases of erysipelas treated with sulfanilamide at the Los Angeles County Hospital from April 1, 1937 to August 1, 1939, is reviewed in detail.

3. The average blood level in 121 cases was 5.8 mg. per 100 c.c.

4. The average period of hospitalization was eight days; the average time for the temperature to reach normal was 48 hours; and the average time for the lesion to regress was 50 hours for all patients treated, and this was approximately the average for all age groups.

5. The gross mortality was 1.3 per cent for the series, which is the lowest mortality rate reported in any series to date of writing.

6. The sulfonamide drugs are the treatment of choice in erysipelas.

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SULFADIAZINE AND SODIUM SULFADIAZINE: A COMPARISON OF CERTAIN OF THEIR CLINICAL AND PHARMACOLOGIC VALUES *

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SULFADIAZINE (2-sulfanilamido-pyrimidine) and sodium sulfadiazine are following sulfathiazole and sodium sulfathiazole in experimental and clinical trial just as these thiazole derivatives followed sulfapyridine and its sodium salt. Already a number of reports [1-10] on the absorption, excretion, acetylation, diffusion, toxicity, and therapeutic effects of sulfadiazine in man have appeared, but because the indication is strong that sulfadiazine and its sodium salt will displace largely the other sulfonamide drugs, additional observations on the pharmacology of this drug seem important.

Previous reports on the pharmacology of sulfadiazine have dealt primarily with the observations made following a single dose of the drug and in a few cases where it has been continued for a short period of time. The findings which we are presenting in this paper are obtained from a large series of patients treated over an extended period of time. In some instances it represents daily observations of blood and urine concentrations correlated with the clinical status of the patient for periods up to two months. Furthermore, in this study we have interested ourselves in sodium sulfadiazine and have used it orally as well as intravenously. Sodium sulfadiazine can be readily administered intravenously, giving almost immediate high blood concentrations. When given in a dosage sufficient to produce blood levels even to 50 mg. per cent, no immediate or subsequent serious toxic reactions followed. After the oral administration of sodium sulfadiazine and sulfadiazine in equal dosage, a comparison of the absorption curves shows that the sodium salt is more rapidly absorbed and its concentration in the blood reaches a higher level. These findings seem to have definite practical significance.

MATERIALS AND METHODS

The patients observed in this study were all adult males and females with body weights within the usual range of 50 to 80 kg., who were patients on the pavilions of The New York Hospital.† They suffered from a variety

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Directed by the Committee on Chemotherapy, Cornell University Medical College, composed of Dr. William DeWitt Andrus, Dr. McKeen Cattell, Dr. Russell L. Cecil, Dr. Vincent du Vigneaud, Dr. Claude E. Forkner, Chairman, Dr. Frank Glenn, and Dr. Norman Plummer.

The drugs used in this investigation were supplied by the Lederle Laboratories, Inc.

† Some infants and children are included in the data relating to the incidence of toxic effects.

of bacterial infections. Pneumonia, acute bronchitis, chronic bronchiectasis, chronic lung abscess, and subacute bacterial endocarditis make up the majority of the included diagnoses. A few of the patients were essentially normal individuals convalescing from transient illnesses of various sorts. None of the patients included for study of the absorption and excretion curves suffered from renal insufficiency, retention of urine, oliguria, congestive heart failure, or other conditions which might disturb the usual readings.

Blood specimens for determinations of drug level were mixed with potassium oxalate to prevent clotting, and both blood and urine specimens were kept in the refrigerator until analysis was made. When blood specimens were taken daily, the blood was drawn at the same time each day (between the hours 8 and 9 a.m.). All determinations of drug in urine and other body fluids were made in the Chemotherapy Laboratory of The New York Hospital by technicians especially trained in this work.

For the measurement of urinary excretion, collection of urine was started at the same time that the first dose of drug was given, and continued after the drug was stopped until only traces were detectable in the urine. All urine specimens were collected individually as voided, and later were put together to make 24-hour specimens. The volume of each urine specimen was measured, and determinations of the concentration of both free and total drug were made on every specimen. When a precipitate of drug was present in a urine specimen, the specimen was shaken well to insure dispersion of the crystals throughout the specimen before a portion was pipetted off for analysis. When collection of a 24-hour specimen was incomplete, the data for that day were discarded.

Determinations of the amounts of drug in urine and body fluids were made by the method of Bratton and Marshall.[11] Except where specifically stated in the text, values for sodium sulfadiazine have not been altered to allow for the difference in molecular weight between sulfadiazine and sodium sulfadiazine.*

Patients who received sulfadiazine or sodium sulfadiazine by mouth were given an initial dose of either 2.0 or 4.0 gm. and then 1.0 gm. every four hours day and night. Sulfadiazine was given in the form of 0.5 gm. tablets and sodium sulfadiazine in gelatin capsules containing 0.5 gm. of the drug. Sodium sulfadiazine for intravenous use was administered as a 5 per cent solution in distilled water, made by diluting the 10 c.c. ampoule of 25 per cent solution supplied by the manufacturer. The dose was usually 2.5 gm., and this was injected intravenously over a period of 5 to 10 minutes. Injections were repeated at varying intervals in different patients, usually between six and eight hours. No local reactions, such as sloughs or venous thromboses, and no general reactions were encountered as a consequence of giving the drug by this method.

* The molecular weight of sodium sulfadiazine is 273. The molecular weight of sulfadiazine is 250.

Absorption into the Blood

Comparison of Sulfadiazine and Sodium Sulfadiazine when Given Orally. Curves, representing the average absorption into the blood following the oral administration of sulfadiazine and sodium sulfadiazine in a dosage of 2.0 gm. initially, followed by 1 gm. every four hours, are shown in figure 1, and the range of these values is shown in table 1. These data show that the values for free and total drug throughout the first 48 hours of treatment are appreciably higher following the use of sodium sulfadiazine. The degree of acetylation is about the same for both drugs.

Influence of the Size of the Initial Dose. While the maintenance dose of 1.0 gm. every four hours has been widely accepted, there has been a great difference of opinion regarding the optimum amount of the initial dose of these drugs. For this reason, we considered it essential to make studies of

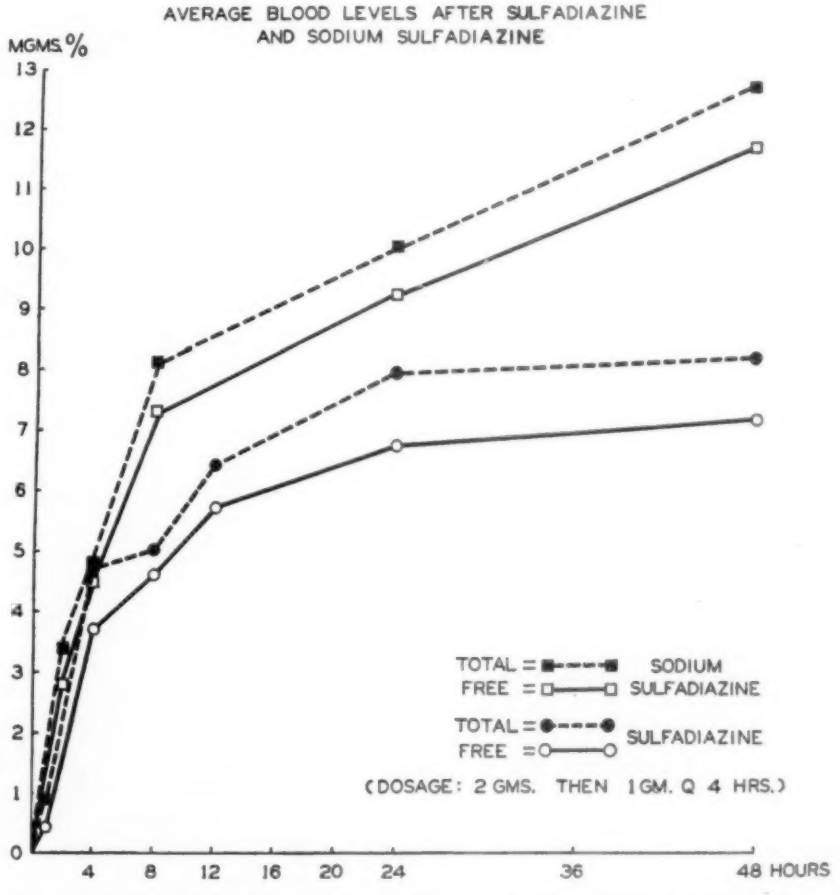

Fig. 1. Concentrations of free and total drug in the blood following the start of continuous per oral treatment with sulfadiazine and sodium sulfadiazine. Each point plotted represents an average of determinations made in at least 10 patients.

TABLE I

Blood Concentrations of Free Drug (in Milligrams Per Cent) Following Continuous Oral Dosage with Sulfadiazine (Dosage: Initial Dose of 2.0 or 4.0 gm., Followed by 1.0 gm. Every 4 Hours)

Hours After First Dose	Sulfadiazine						Sodium Sulfadiazine					
	Initial Dose 2.0 gm. (10 patients)			Initial Dose 4.0 gm. (14 patients)			Initial Dose 2.0 gm. (10 patients)			Initial Dose 4.0 gm. (11 patients)		
	Low	High	Average	Low	High	Average	Low	High	Average	Low	High	Average
1	0.0	1.4	0.4	—	—	—	—	—	—	—	—	—
2	—	—	—	1.2	6.4	4.0	trace	5.0	2.8	3.1	14.2	6.7
4	1.4	7.4	3.8	2.4	8.3	6.3	1.8	9.3	4.5	5.5	14.8	7.9
8	2.2	9.6	4.6	—	—	—	3.7	12.5	7.3	—	—	—
12	3.1	9.0	5.7	—	—	—	—	—	—	—	—	—
24	4.4	10.2	6.7	—	—	—	5.7	16.6	9.2	—	—	—
48	6.6	10.6	7.1	—	—	—	5.4	16.6	11.6	—	—	—

the absorption into the blood after a larger initial dose. Accordingly, determinations of the levels of free and total drug were made at two- and four-hour intervals after the oral administration of 4.0 gm. of sulfadiazine and of 4.0 gm. of sodium sulfadiazine. The average blood levels observed following these doses are shown in figure 2, and the range of values in table 1. Comparison of the levels in the blood following 2.0 and 4.0 gm. doses of both drugs (figures 1 and 2, and table 1) reveals that the 4.0 gm. dose yields considerably higher levels at the end of both two and four hours in each case. Table 1 shows that there is marked variation in individual patients with respect to the levels of drug observed in the blood following identical doses of the same drug. In this respect, no particular difference was noted between the absorption of the base or the sodium salt. Determinations after the larger initial doses again showed that the acetylation was almost the same after the administration of the two different preparations.

Observations during Prolonged Treatment. The duration of treatment of the patients studied is shown in table 4. Analysis of the data regarding the blood concentrations in the 147 patients who received continuous oral dosage of sulfadiazine and the 50 who received similar dosage of sodium sulfadiazine shows that blood concentrations of free drug of between 8 and 12 mg. per cent were usually obtained following the use of sulfadiazine, and of between 12 and 15 mg. per cent following sodium sulfadiazine. In the instance of sulfadiazine, the proportion of drug present in the blood in the acetylated form averaged about 10 per cent of the total, while in that of sodium sulfadiazine the value was 13 per cent. It was observed also that after the first 48 hours of treatment neither the concentration of free drug nor the degree of acetylation increased. Regardless of the duration of treatment, when the drugs were withdrawn, the blood level of total drug fell to about 2.0 mg. per cent within 36 to 48 hours and to a trace by the end of 72 hours. The blood level maintained in different patients receiving the

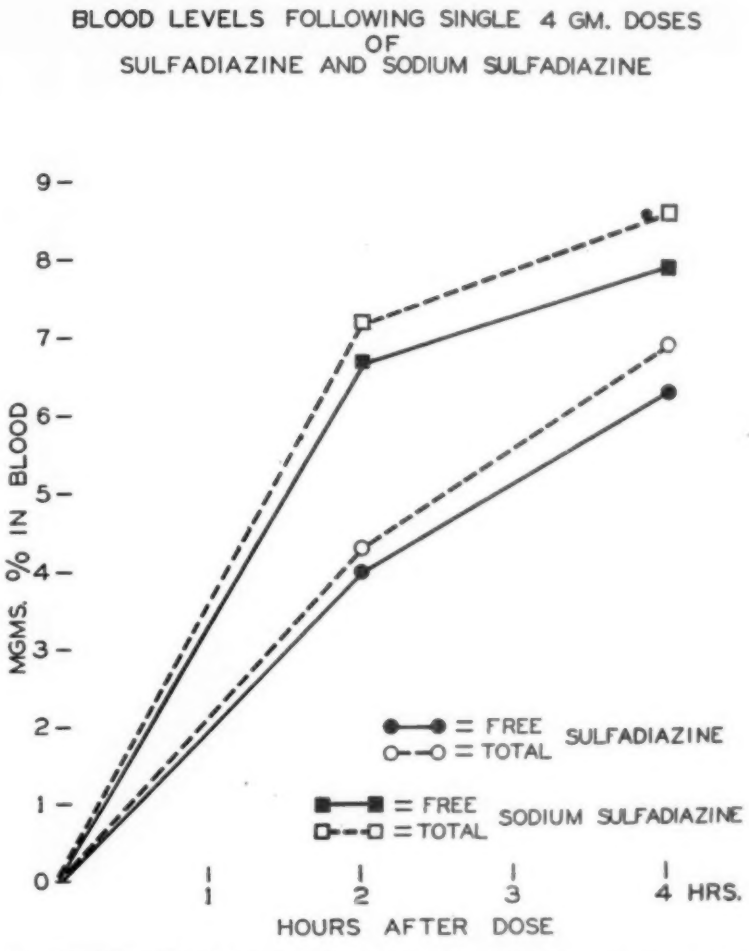

FIG. 2. Concentrations of free and total drug in the blood at intervals of 2 and 4 hours after single doses of 4 gm. of sulfadiazine and sodium sulfadiazine given by mouth. Each point plotted represents an average of determinations made in at least 10 patients.

same dosage of drug varied considerably. A considerable variation in the per cent conjugated was observed in the same patient at different times. An occasional patient on some days exhibited conjugation as high as 20 to 30 per cent, whereas on other days the conjugated fraction was imperceptible. No patients were encountered who consistently showed more than 15 per cent of acetylated drug in the blood following the administration of either sulfadiazine or its sodium salt.

Intravenous Use of Sodium Sulfadiazine. Intravenous injections of sodium sulfadiazine were given to 21 patients, the individual dose being 2.5 gm. One patient received 13 injections, three patients 8, two patients 6, thirteen patients from 2 to 4 injections, and two patients received only a single treatment. The interval between injections was usually from 4 to 10

hours, depending upon the exigencies of the case. The curves of blood levels for 24 hours following single doses of 2.5 gm. of sodium sulfadiazine given intravenously are shown in figure 3. Following the administration of repeated doses by intravenous injection, in individual patients there is marked and unpredictable variation in the blood concentrations. Some patients at a given time exhibited levels of 30 to 40 mg. per cent of the total drug, while others who had received identical dosage of drug and in whom the levels were taken at comparable times in relation to the doses showed levels of only 10 to 15 mg. per cent of total drug. For example, Patient C. A. received

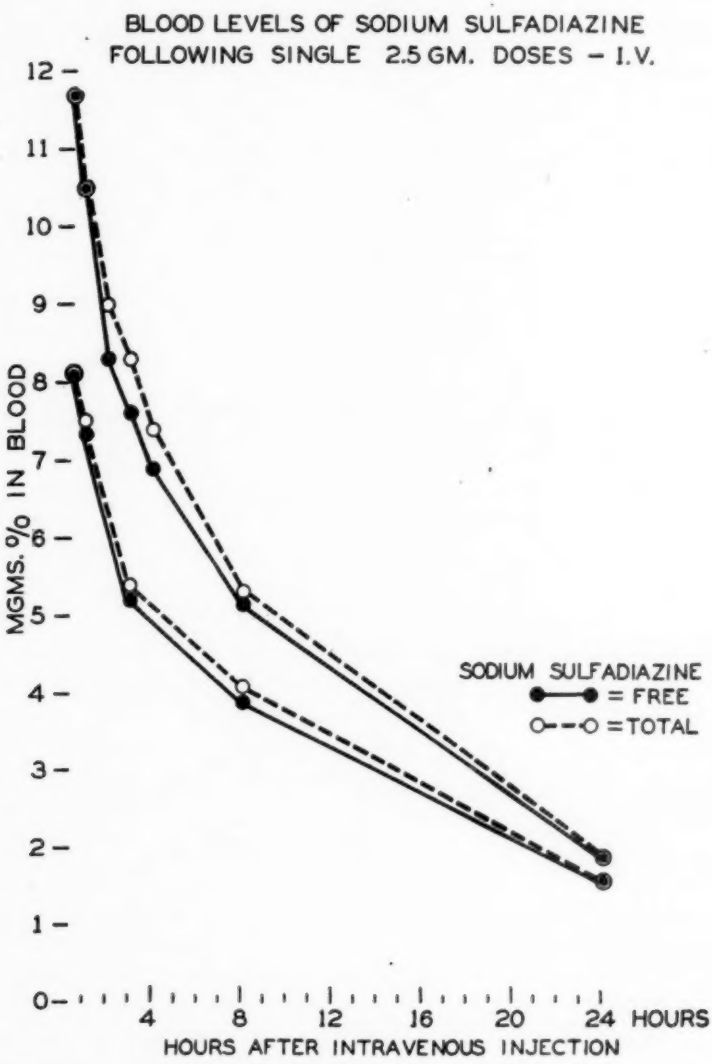

FIG. 3. Concentrations of free and total drug in the blood after an intravenous injection of 2.5 gm. of sodium sulfadiazine. The values observed in 2 patients are represented.

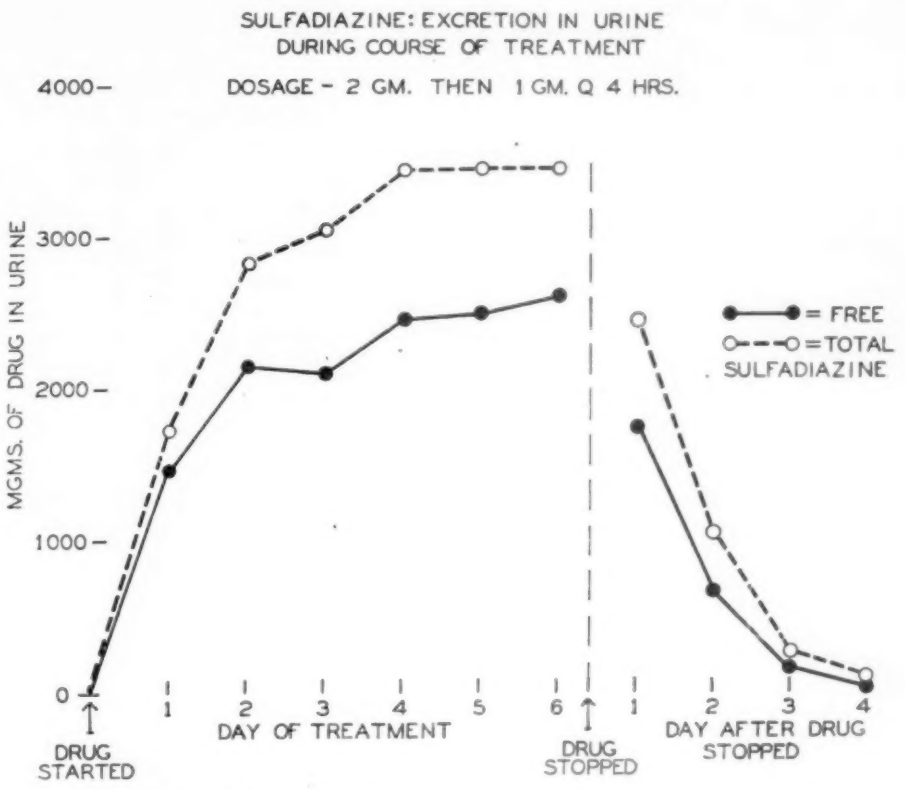

FIG. 4. Amounts of free and total drug excreted daily in the urine during the course of continuous per oral treatment with sulfadiazine, 1 gm. every 4 hours. The excretion of the drug after treatment was stopped is represented on the right hand side of the figure. Each point plotted represents an average of determinations made in from 10 to 22 patients.

an initial dose of 2.5 gm. and three additional doses at intervals of 4, 12, and 20 hours after the initial injection, making a total of 10 gm. in 20 hours. A blood level was taken 17 hours after the last injection, and this was 44.4 mg. per cent of total drug. On the other hand, Patient G. A received the same dosage of drug at the same intervals of time, but in this instance a blood level taken 17 hours after the last injection was only 12.9 mg. per cent of total drug. In general, we observed that two injections at an interval of 4 to 6 hours followed by subsequent injections every 8 to 12 hours provided levels rarely above 20 mg. per cent just after an injection or below 10 mg. per cent shortly before the next injection. When injections were continued at intervals of four to six hours, blood levels of 40 to 50 mg. per cent of the free drug were observed usually after the third or fourth injection. It is important to emphasize the unpredictable way in which individual patients behave following intravenous therapy, and to advise that frequent determinations of the blood levels be made when more than a single injection of the drug is given.

The proportion of the drug present in the conjugated form following intravenous administration is usually less than that observed following oral treatment. It is generally less than 5 per cent of the total, but in rare instances is as high as 30 per cent. Again, when intravenous treatment is continued for several days, there is no tendency for the conjugated fraction to increase over that which occurs shortly after the start.

Urinary Excretion of Sulfadiazine and Sodium Sulfadiazine

The urinary excretion of sulfadiazine and sodium sulfadiazine was studied throughout the course of per oral treatment in 22 patients who received an initial dose of 2 gm. of sulfadiazine followed by 1 gm. every four hours, and in another 22 patients who received identical dosage of sodium sulfadiazine. The average length of time during which these patients received the drugs was six days, but in a few patients it was possible to continue observations over periods as long as 28 days. The urinary excretion of the two drugs was in general the same (figures 4 and 5). The amount

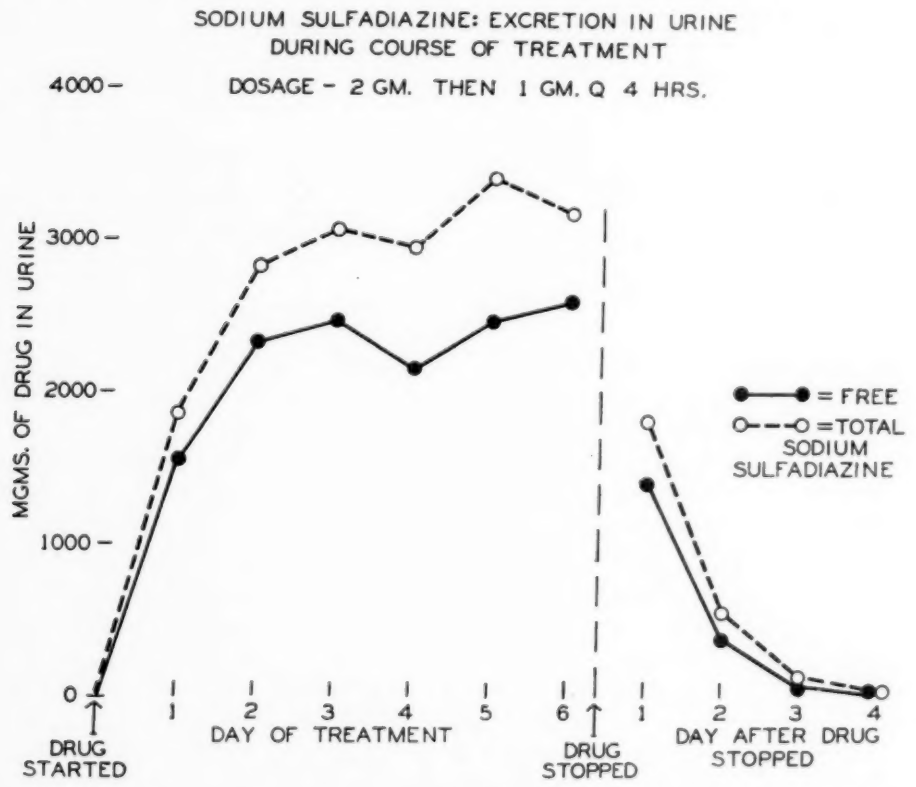

Fig. 5. The same data shown in figure 4 for sulfadiazine are represented here for sodium sulfadiazine. In this figure also, each point plotted represents an average of determinations made in from 10 to 22 patients.

TABLE II

Daily Volume of Urine, Urinary Excretion, and Blood Concentration During Treatment with Sulfadiazine and Sodium Sulfadiazine

Day of Treatment	B.R., male, aged 34 years. Subacute Bacterial Endocarditis						L.E., male, aged 45 years. Subacute Bacterial Endocarditis						S.T., male, aged 43 years. Subacute Bacterial Endocarditis						B.U., male, aged 21 years. Meningococcus Meningitis						C.O., female, 24 years. Lobar Pneumonia						T.U., female, 26 years. Pyelitis				
	Dose of Drug* (Gm.)	Concentration of Drug (Mg. %)				24 Hr. Urine Vol. (liters)	Dose of Drug* (Gm.)	Concentration of Drug (Mg. %)				24 Hr. Urine Vol. (liters)	Dose of Drug* (Gm.)	Concentration of Drug (Mg. %)				24 Hr. Urine Vol. (liters)	Dose of Drug* (Gm.)	Concentration of Drug (Mg. %)				24 Hr. Urine Vol. (liters)	Dose of Drug* (Gm.)	Concentration of Drug (Mg. %)				24 Hr. Urine Vol. (liters)	Dose of Drug* (Gm.)	Concentration of Drug (Mg. %)				24 Hr. Urine Vol. (liters)
		Blood		24 Hr. Urine				Blood		24 Hr. Urine				Blood		24 Hr. Urine				Blood		24 Hr. Urine				Blood		24 Hr. Urine				Blood		24 Hr. Urine	
		Free	Total	Free	Total			Free	Total	Free	Total			Free	Total	Free	Total			Free	Total	Free	Total			Free	Total	Free	Total			Free	Total	Free	Total	
1	2 iv	11.7	11.7	96	112	1.6	6 SS	—	—	—	—	—	5 iv, 3S	8.1	8.1	167	190	0.4	4 S	—	—	—	—	—	4 SS	7.5	7.9	172	192	1.4	6 S	—	—	143	143	1.7
2	0.	1.9	1.9	31	41	1.8	"	10.8	11.1	276	348	1.0	6 S	10.0	11.1	200	308	1.1	6 S	—	—	—	—	—	6 SS	10.2	10.7	152	190	1.9	"	7.0	7.7	200	238	1.1
3	2 iv, 6 SS	13.7	15.3	76	88	1.7	"	—	—	308	348	0.9	"	12.1	12.5	200	267	1.0	"	4.2	4.4	160	222	1.1	"	15.3	15.7	112	145	2.4	"	8.8	10.8	168	258	1.2
4	6 SS	15.0	18.1	174	200	0.5	"	12.1	15.3	372	381	0.7	"	11.1	11.7	108	148	2.4	"	4.4	4.7	167	286	0.5	"	22.2	22.4	93	118	1.7	"	8.1	8.3	216	333	2.6
5	2 iv, 6 SS	14.8	15.0	270	325	0.9	7 SS	—	—	381	381	0.9	"	12.9	12.9	114	154	2.0	"	—	—	216	308	0.5	"	14.7	14.9	160	222	1.8	"	8.0	8.1	—	—	—
6	" "	20.4	22.2	180	329	0.5	"	13.3	13.5	444	460	1.0	"	12.5	13.3	—	—	—	"	4.8	5.7	95	118	2.6	"	15.3	15.8	160	182	1.8	"	11.4	11.4	123	190	1.3
7	" "	29.6	38.0	194	238	0.8	"	—	—	457	533	0.6	"	8.0	9.0	—	—	—	"	6.4	7.0	138	190	1.6	"	15.3	16.3	133	160	2.8	"	8.3	8.3	—	—	—
8	2 SS	27.4	28.5	260	318	1.8	"	—	—	533	615	1.0	"	7.0	7.8	—	—	—	"	5.1	5.7	140	200	1.0	"	13.3	14.8	118	143	1.7						
9	2 iv, 2 SS	8.3	8.4	180	223	0.8	5 SS	—	—	592	666	0.9	"	8.6	9.3	—	—	—	"	5.4	5.7	98	125	1.6	"	—	—	205	211	1.5						
10	6 SS	14.2	16.0	188	235	1.2	"	14.5	16.2	500	571	0.6	"	7.1	7.5	222	250	1.6	"	5.4	5.9	154	235	1.2	"	15.3	17.3	190	200	1.3						
11	"	13.7	14.0	203	230	2.3	"	—	—	410	470	0.7	"	6.2	6.5	174	250	0.9	"	6.5	7.5	—	—	—												
12	"	17.3	17.4	210	287	0.7	"	15.0	20.0	302	372	0.6	"	7.6	7.6	286	364	1.2	"	6.0	7.1	200	296	1.5												
13	"	17.3	17.3	143	182	0.8	"	—	—	271	332	0.6	"	9.0	9.3	286	400	1.1	"	7.2	7.4	133	190	1.8												
14	"	14.2	15.3	205	222	1.7	"	—	—	280	533	0.8	"	7.1	7.4	250	308	1.1	"	6.3	6.4	108	190	1.1												
15	"	14.2	14.7	174	242	1.0	"	12.8	14.2	320	421	0.9	"	7.0	7.0	167	200	1.8	"	7.1	7.1	98	148	1.8												
16	"	12.1	12.5	190	210	1.1	"	19.0	20.0	313	372	0.9	"	7.5	7.6	200	235	1.8	2.5 iv, 6 S	6.6	7.0	121	160	1.0												
17	"	14.8	15.0	125	133	2.1	"	—	—	286	364	0.9	"	8.0	8.0	160	200	2.0	" "	13.3	13.7	—	—	—												
18	"	15.3	15.5	118	148	1.3	"	12.9	13.4	254	267	1.2	"	7.5	8.6	190	250	1.6	6 S	7.5	8.6	65	133	1.5												
19	"	12.1	12.5	167	170	1.2	"	—	—	266	276	1.2	"	7.2	7.8	211	253	1.5	"	7.1	8.6	87	174	1.6												
20	"	15.3	15.8	190	190	1.5	6 SP	—	—	235	320	0.8	"	7.0	7.4	211	250	1.1	"	—	—	70	148	1.3												
21	"	14.8	15.0	228	267	1.3	"	—	—	262	364	0.5	"	6.7	7.1	167	200	1.9																		
22	"	12.9	13.5	200	216	1.1	"	14.7	16.6	372	533	0.5	"	7.0	7.2	133	174	2.0																		
23	"	12.5	13.3	200	267	1.2	10 SP	—	—	340	552	0.4	"	7.1	9.7	190	200	2.0																		
24	3 SS, 3 S	12.9	13.1	151	182	2.4	8 SP	—	—	444	850	0.4	"	6.7	8.8	121	167	2.8																		
25	6 S	12.5	12.9	170	182	1.7	0	—	—	533	701	0.3	"	5.9	8.0	—	—	—																		
26	"	14.2	15.3	170	182	0.8																														
27	"	13.3	14.2	157	182	1.2																														
28	"	13.7	15.3	170	228	1.3																														
29	"	16.0	17.3	—	—	—																														

* iv = Sodium Sulfadiazine intravenously. SS = Sodium Sulfadiazine orally. S = Sulfadiazine orally. SP = Sulfapyridine orally.

was as low as 1 gm. or as high as 8 gm. in a single 24-hour period, but averaged about 3.5 gm. The concentration of drug in the 24-hour urine specimen was roughly proportional to the daily volume of urine. After the third day of treatment the concentration of total drug in the 24-hour urine specimen usually remained between 200 and 300 mg. per cent. There appeared to be no relationship between the total amount of drug excreted daily in the urine and the daily volume of urine unless this exceeded 2000 c.c. When the daily excretion of drug in the urine exceeded 4 gm., it was usually in association with a 24-hour urine volume of more than 2000 c.c., and whenever exceptionally large amounts of the drugs, such as 6 to 8 gm., were excreted in the urine in a single day, the volume of urine on that day usually exceeded 3000 c.c. These data are illustrated in table 2.

When administration of the drugs was stopped, excretion of the drug remaining in the body or unabsorbed in the gastrointestinal tract was rapid (figures 4 and 5). In rare instances the excretion was prolonged for as long as eight days, even though the urinary output during this period was as good as the average for the group. The time required to excrete all of the drug after administration was stopped was essentially the same regardless of the duration of treatment.

The per cent conjugated averaged 30 per cent for the patients who received sulfadiazine and 23 per cent for those who received sodium sulfadiazine. Only an occasional patient maintained more than 50 per cent of the acetylated drug in the urine, and many never exhibited more than 15 per cent. No tendency to increase the conjugation was observed when treatment was continued as long as four weeks (table 2). An average of about 60 per cent of the total amount of drug given was recovered from the urine in the case of both drugs, the range of values being from 43 to 85 per cent.*

The urinary excretion of the drug in the 21 patients who received sodium sulfadiazine intravenously was also studied. The concentrations of total drug observed in the urine of these patients rarely exceeded 300 mg. per cent even when the blood level of total drug was 30 to 40 mg. per cent. It was usually between 100 and 200 mg. per cent, when injections were being given at intervals of four to six hours. The proportion of drug conjugated varied from 3 to 60 per cent in the same patient at different times, but was usually between 20 to 30 per cent. In a single patient in whom collection of urine was complete, 90 per cent of the drug was recovered in the urine over a period of 48 hours following a single injection of 2.5 gm.

Diffusion of Sulfadiazine

In nine patients simultaneous determinations of the concentration of sulfadiazine in the blood and cerebrospinal fluid were made during the course of treatment. In three of these the concentration of total drug was higher

* These data are based on correction of the data relating to sodium sulfadiazine for the difference in molecular weight between sulfadiazine and sodium sulfadiazine.

TABLE III
Age Distribution of 218 Cases Treated with Sulfadiazine and Sodium Sulfadiazine

Age (Years)	Number of Cases Treated		
	Sulfadiazine Orally (1 gm. q. 4 hr.)	Sodium Sulfadiazine	
		Orally (1 gm. q. 4 hr.)	Intravenously (see text)
0– 1	3	0	1
1– 5	6	0	2
5–15	7	2	1
15–25	28	4	3
25–40	35	12	6
40–60	46	22	6
60–80	22	10	2
Total Cases	147	50	21

in the cerebrospinal fluid than in the blood,* and in the other six cases it varied between 49 and 100 per cent of that in the blood, averaging 72 per cent. The concentrations of total drug in the cerebrospinal fluids of these patients varied between 2 and 17.3 mg. per cent, averaging 7.5 mg. per cent. In three patients simultaneous determinations of the concentration of sulfa-

TABLE IV
Distribution of 218 Cases Treated with Sulfadiazine and Sodium Sulfadiazine According to Duration of Treatment

Duration of Treatment (Days)	Number of Cases Treated		
	Sulfadiazine Orally (1 gm. q. 4 hr.)	Sodium Sulfadiazine	
		Orally (1 gm. q. 4 hr.)	Intravenously (see text)
1– 2	2	16	
3– 7	62	21	
7–14	52	11	
14–21	18	2	
21–28	8	0	
28–35	2	0	
35–42	2	0	
63–72	1	0	
Total Cases	147	50	21

diazine in the pleural fluid and in the blood were made during the course of treatment. In these three cases, the concentrations of total drug in the pleural fluid were 74, 90, and 91 per cent of those in the blood, and the concentrations of total drug in the pleural fluid were 15.7, 4.6, and 11.7 mg. per cent respectively. In a single patient simultaneous determinations of the

*Every effort was made to avoid contamination of the specimens with novocaine, but the possibility remains that such contamination did occur and that this explains the finding of higher concentrations in the cerebrospinal fluid than in the blood.

concentration of sulfadiazine in ascitic fluid and in blood were made, a concentration of total drug of 4.0 mg. per cent in the ascitic fluid, and of 5.7 mg. per cent in the blood being observed.

Incidence and Nature of Toxic Reactions

The distribution of the patients included in this study according to age and duration of treatment is shown in tables 3 and 4. The nature and a few

Table V

Toxic Reactions Occurring in 218 Cases

Case No.	Age in Yrs.	Sex	Diagnosis	Type of Reaction	Day of Treatment Reaction Occurred	Amount of Drug Given when Reaction Occurred Grams	Blood Level on Day Reaction Occurred mg. %	
							Free	Total
Cases Treated with Sulfadiazine								
1	26	F	Lobar pneumonia	Pain in both flanks and gross hematuria	4	17	4.4	—
2	75	F	Bronchopneumonia	Pain in both flanks and gross hematuria	8	41	20.0	21.0
3	62	F	Carcinoma of esophagus; postoperative wound infection	Gross hematuria (no pain in flank)	3	11	12.5	—
4	52	M	Pulmonary tbc., acute bronchitis	Pain in left flank; gross hematuria	8	43	14.5	20.0
5	46	F	Sinusitis; bronchial asthma	Skin eruption	13	64	12.5	—
6	23	F	Acute pharyngitis (Beta hemo. strep.)	Skin eruption	9	38	8.8	11.1
7	21	M	Meningococcal meningitis	Skin eruption	9	51	—	—
8	23	M	Subacute bacterial endocarditis	Pyrexia of 39.6° C. Fall in WBC from 7600 to 2400	23	131	10.6	—
9	52	F	Dermatitis	Pyrexia of 39.6° C.	9	20	7.2	—
10	43	M	Subacute bacterial endocarditis	Mild peripheral neuritis	16	95	7.5	7.6
Cases Treated with Sodium Sulfadiazine								
11	9	F	Scarlet fever	Pain in right flank; gross hematuria	1	8	11.7	12.5
12	50	F	Lobar pneumonia	Pain in left flank; gross hematuria	8	40	8.5	9.7
13	45	M	Subacute bacterial endocarditis	Skin eruption	9	55	13.3	13.5
14	6	F	Scarlet fever	Skin eruption	6	15	5.4	7.1
15*	43	M	Subacute bacterial endocarditis	Skin eruption	2	SD16 SSD 5	10.1	11.1
16†	21	M	Meningococcal meningitis	Stomatitis	16	SD96 SSD 5	7.5	8.6

* Two intravenous injections of 2.5 gm. of sodium sulfadiazine given on day before skin rash appeared, in addition to 16 gm. of sulfadiazine given by mouth before rash appeared.

† Two intravenous injections of 2.5 gm. of sodium sulfadiazine given on day before stomatitis appeared, in addition to 96 gm. of sulfadiazine which had been given by mouth.

details of the toxic reactions which we encountered in this same group following treatment with sulfadiazine and sodium sulfadiazine orally and the latter drug intravenously are presented in table 5. There was an almost complete absence of nausea and vomiting following the administration of these drugs. Only two patients, not included in table 5 and both following the use of sulfadiazine orally, exhibited this reaction. Even in those patients who exhibited blood concentrations of total drug of between 20 and 50 mg. per cent, nausea and vomiting did not occur. Decrease in the amount of hemoglobin and the count of the red blood cells, cerebral effects, agranulocytosis, jaundice or other evidence of hepatitis, and cyanosis were not recognized during the course of treatment with these drugs in this series of cases.

The toxic effects did not result seriously in any instance, and subsided promptly in every case when the drugs were discontinued. The toxic effects on the kidneys perhaps should be regarded as the most serious of those encountered. In the patients who experienced colic, the pain occurred both unilaterally and bilaterally, was never severe, and did not persist for more than 12 hours. Gross hematuria was noted usually in only a single urine specimen, and in every instance subsided at the end of 24 hours. Not one patient who had experienced the toxic effect on the kidneys showed evidence of permanent renal damage. In every instance the urinalysis and renal function, as measured by ability to concentrate the urine and the urea clearance test, were normal within a few days of the time that the reaction occurred. Other patients during the course of treatment exhibited a slight or moderate increase in the number of red blood cells observable on microscopic examination of the centrifugized urine sediment. This was usually in association with considerable numbers of crystals of drug. This finding was not regarded as an indication for withdrawing the drug, and when it was continued in such cases no ill effect was observed. The skin eruptions were generalized and macular or morbilliform in character, similar to those observed with other sulfonamide drugs. There was no associated fever, and in no case did exfoliation of the skin occur. The rash subsided promptly when the drug was discontinued.

Discussion

Our data indicate that continuous oral dosage of sulfadiazine results in higher blood concentrations of free drug than are usual following the same dosage of sulfapyridine [12, 13, 14] or sulfathiazole,[15, 16] and the values which we observed following the use of sodium sulfadiazine are even higher than those for sulfadiazine itself. These differences are illustrated in figure 6. The differences between the values observed for sulfadiazine and sodium sulfadiazine are similar to those reported for sulfapyridine [17, 18, 19] and sulfathiazole [17, 19] and their sodium salts.

The proportion of acetylated drug present in the blood following the oral administration of sulfadiazine and both oral and intravenous admin-

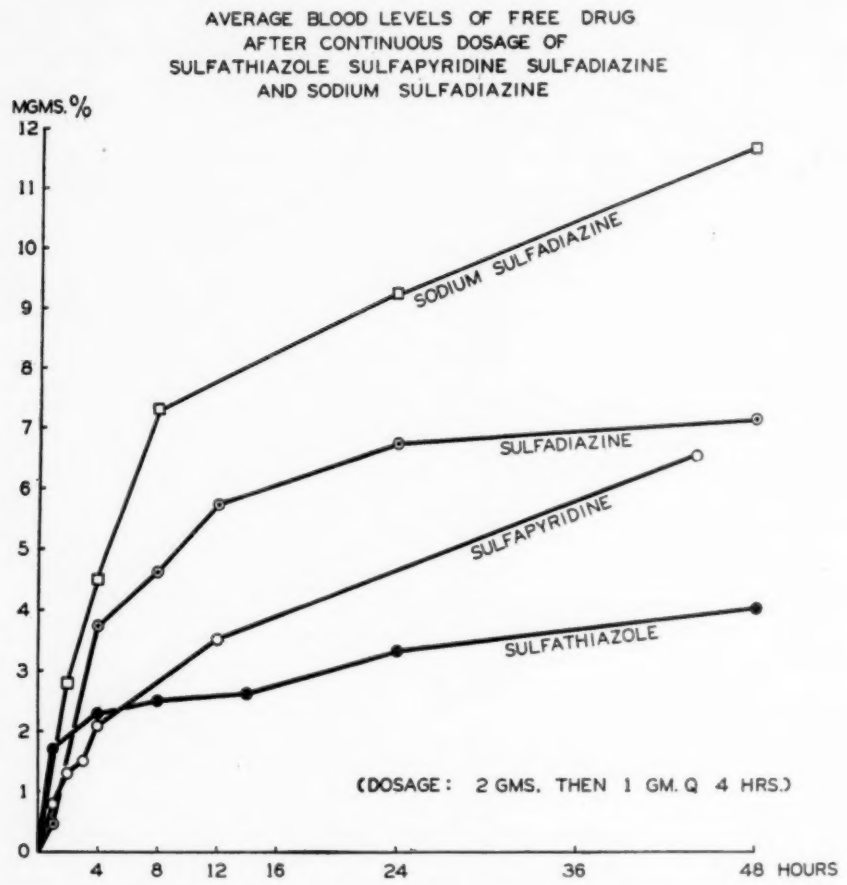

FIG. 6. Concentrations of free drug in the blood after the same continuous peroral dosage of sulfapyridine, sulfathiazole, sulfadiazine, and sodium sulfadiazine. In the instances of sulfadiazine and sodium sulfadiazine, each point plotted represents the average of determinations made in at least 10 patients. The values represented for sulfapyridine are those reported by Kinsman, Moore and Harrison in the Journal of Laboratory and Clinical Medicine (1940, xxv, 1235).

istration of sodium sulfadiazine was much smaller than that usually observed after sulfapyridine [20, 21, 22] and sulfathiazole [5, 16] and their sodium salts. Furthermore, acetylation did not increase during prolonged therapy, as has been observed in the instances of sulfanilamide [23] and sulfapyridine.[19, 22] In this respect, sulfadiazine behaved very much like sulfathiazole.[19] Similarly the proportion of acetylated drug present in the urine following the use of sulfadiazine and sodium sulfadiazine was much less than that observed after the use of sulfanilamide [21, 23, 24] or sulfapyridine,[21, 25] and slightly less than that observed after sulfathiazole.[15, 26] The difference between sulfadiazine and sulfapyridine in the proportion of drug excreted in the urine in the acetylated form is well shown by Patient L. E. in table 2. On the twentieth day of treatment, sulfadiazine was discontinued and sulfapyridine given instead.

Synchronous with this change in the medication, the proportion of drug present in the acetylated form increased from less than 5 per cent to as high as 50 per cent. Again, because the relationship between the amount of drug acetylated and the production of toxic effects, sulfadiazine may possess an advantage with respect to the small percentage of acetylated drug excreted in the urine.

The data which we have available do not allow many conclusions regarding the explanation of the variations which different patients and the same patient at different times, receiving the same dose of drug, exhibit in the concentration of drug in the blood or the amount of drug excreted in the urine. There probably is a variation in the absorption of drug from the gastrointestinal tract, but the factors influencing this difference are not recognized. Similarly, there appears to be no explanation for the variations in conjugation and no definite lead to the factors influencing it. The concentration of total drug in blood or urine appeared to have no influence on acetylation. Age or sex of patient, concomitant disease, degree of pyrexia, and other similar factors appeared to have no influence on the variations described.

The data which we have presented regarding the concentration of sulfadiazine in cerebrospinal fluid and other body fluids, indicate that this drug, like sulfanilamide and sulfapyridine, and unlike sulfathiazole, is readily diffused.

There were proportionately few toxic reactions following the use of diazine derivatives. Our data do not allow many conclusions regarding the factors involved in the production of the few toxic reactions which we observed. It does not appear possible to correlate the occurrence of reactions with age, sex, diagnosis, fluid intake, urinary output, concentration of drug in the blood, or proportion of the drug acetylated. Although the blood levels observed in some patients at the time of a toxic reaction were higher than the average, in others they were lower. A number of patients who had high levels either transiently or over long periods of time never experienced any toxic effect. Only one patient (Case 2, table 5) out of a group of 15, who at one time or another exhibited a blood concentration of total drug of 15 mg. per cent or higher following administration of sulfadiazine or sodium sulfadiazine, developed a toxic reaction. Our data are of particular interest relating to the occurrence of pain in the flank and gross hematuria. In two patients (Cases 4 and 12, table 5), this reaction occurred during the course of studies of the urinary excretion of drug. But in both cases the daily volume of urine, the concentration of total drug in the urine, and the proportion of acetylated drug in the blood and urine revealed no significant differences from the usual findings in our other patients. The readings were within the average range both on the day on which the reaction occurred, and on the days preceding and following. Furthermore, this renal irritation was not noted in any of the patients who exhibited unusually high values for either the concentration of total drug in the urine (as high as 600 mg. per

cent) or proportion of drug acetylated in the urine (as high as 60 per cent). In a third patient (Case 11, table 5), the urine on the day following the occurrence of flank pain and hematuria, and on all subsequent days during the course of treatment, was within the average range for all determinations mentioned above, but unfortunately it was not studied on the days preceding the reaction. These findings suggest that the renal toxic effects following the use of these drugs, and possibly other types of reactions, occur on some other basis than on that of unusual concentration in the blood or urine or degree of acetylation.

Summary and Conclusions

1. The absorption, excretion and acetylation of sulfadiazine, given orally, and of sodium sulfadiazine, given both orally and intravenously, have been studied in 218 patients who received these drugs over long periods of time. The toxic effects which occurred in these patients have been correlated with the pharmacological data available.

2. Sulfadiazine given orally yields higher concentrations of drug in the blood and smaller proportions of acetylated drug in the blood and in the urine than do any of the other sulfonamide drugs in general use except sulfonamide. This is a confirmation of earlier reports.

3. Sodium sulfadiazine after oral administration yields even higher concentrations of drug in the blood than does sulfadiazine, and like the latter is acetylated to only a slight degree in the blood and in the urine.

4. Initial doses of 4 grams of sulfadiazine and of sodium sulfadiazine were observed to be much more effective than initial doses of 2 grams in establishing high concentrations in the blood soon after the start of treatment.

5. Sodium sulfadiazine given intravenously yields high levels of drug in the blood, is acetylated to only a slight degree, and appears to be relatively non-toxic.

6. Toxic reactions after sulfadiazine treatment were less frequent and less serious than after the use of other sulfonamide drugs. This, together with the high concentration of free drug obtainable in the blood, suggests that pharmacologically sulfadiazine and sodium sulfadiazine possess definite advantages over the other sulfonamide drugs in general use.

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THE ADVANTAGES AND CLINICAL USES OF DESICCATED PLASMA PREPARED BY THE ADTEVAC PROCESS *

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THE permanent establishment and widespread use of intravenous plasma therapy are now fully realized. It has become apparent that this type of therapy is very efficacious in the handling of many pathological states, the outstanding one of which is shock. The present war and the urgencies of national defense have increased markedly the interest in this field principally because of its tremendous possibilities in military medicine. For these reasons it is the object of this communication to relate the importance of large volume production of desiccated plasma and the experience gained from its clinical use in a routine hospital service during the 21 months of its operation.

At the present time there are differences of opinion as to the concentration of plasma most desirable for use intravenously. Various concentrations have been advocated, including dilute or half-strength plasma,[1] normal or isotonic plasma [2] and concentrated or hypertonic plasma.[3] It has been suggested that the concentration used be based on the state of hydration of the tissues.[4] It is our belief, for reasons to be given subsequently, that concentrated or hypertonic plasma offers more advantages therapeutically, than other forms of plasma commonly used.

In this respect a minor feature of desiccated plasma is the choice of concentration it offers, that is, from the most dilute form of plasma up to four or five times normal concentration. This may be readily obtained by varying the amount of water or saline used as a solvent. But, of far greater value are its technical and therapeutic advantages.[3d] For civilian and military emergencies it offers the necessary ideal storage and transportation facilities. More important, however, are the therapeutic advantages to be mentioned later in regard to shock therapy, control of plasma protein level and adjustment of abnormal fluid balance through its concentration and increased osmotic properties.

The literature on this subject continues to expand rapidly. The various reports are of a dual nature, dealing with methods of production and results of use. The importance of plasma proteins introduced as normal or isotonic plasma in shock has been emphasized by several from experimental evidence.[5] The value of concentrated proteins has been demonstrated by others.[6, 5c, d] One report considers normal and concentrated serum of equal value in shock.[5d] Animal experimentation has also revealed evidence supporting

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plasma protein therapy in burns,[7] wound healing,[8, 3g] liver damage,[9, 8c] massive exudations,[10] intestinal obstruction,[11] starvation,[12] increased intracranial pressure,[13] and edemas.[14] To supplement this there is a growing support of its importance in corresponding clinical conditions.[15, 14b, 8c, 3e, 1c] In the various reports normal or isotonic plasma has been used more widely than hypertonic plasma. This is possibly due to limited facilities in the past for desiccating routinely large volumes of plasma. Hypertonic plasma is being increasingly used and there are definite indications that it possesses important inherent qualities.

Methods

The methods of dehydrating plasma without denaturation of its proteins fall into two major categories, those drying from the frozen state and those drying from the liquid state. The former group utilizes high vacuums under which conditions immense volumes of water vapor are given off. This water vapor must be removed for dehydration to continue and here lie the basic differences between the various apparatuses used. At the present time there are four major principles used in removing this water vapor, namely chemical absorption,[16] cold surface condensation of water vapor,[17, 16b] physical adsorption [3b] and large sized vacuum pump with means to continuously separate water out of the oil.[18] The methods for liquid state drying are numerous [19] and so far have failed to reveal the ability to handle effectively mass production quantities.

Ninety-two per cent of the plasma used in the present series was first desiccated by the adtevac process.[3b] The remaining 8.0 per cent consists of unprocessed normal plasma given intravenously. The methods of handling the plasma have been previously described [3b, d] and only the major steps will be mentioned. Blood is collected into vacuum type bottles. Plasma is obtained either from blood collected expressly for this purpose or from outdated bank blood. The plasma is separated from cells by means of two De Laval separators arranged in series. The entire volume of blood separated each time, 25 to 50 liters, is pooled together to remove the agglutinins. By this method true plasma yields of 50 per cent can be repeatedly obtained in relatively a few minutes' time. Double centrifugation makes for a clear product with most of the fat content removed. At this point plasma is either frozen and used later or filtered and used at once. Filtration is performed by means of a Seitz bacterial filter. An important feature of this step is the use of Filter cel.* This substance, which has been used by commercial veterinarian biological concerns for years, makes for an improved product. It encourages filtration and prevents plugging of the filter pad; it removes a great deal of the fibrinogen thus decreasing future fibrin precipitation and it helps to remove lipoid particles. Since we have successfully filtered plasma obtained from 1,190,000 c.c. of blood, we totally disagree with

* A product of Johns-Manville Sales Corporation, New York, N. Y.

Strumia [2e] on this point. From the filter receptacle plasma is immediately placed in large glass ampoules, attached to the adtevac machine and dried from the frozen state. After 24 to 36 hours it is granulated and dispensed into vaccine type bottles by means of a hopper. This final step reduces the size of the container considerably thus making the dispensing package of practical size. A vacuum is drawn in the bottles so as to encourage the entrance of pyrogen free water which is used as the solvent. Each stage of this partially opened method is checked by bacterial cultures. The use of an air conditioned, dust-free room is an added safeguard.

Desiccated plasma produced in this manner is a porous, friable powder of light amber color occasionally having a pink cast. Even with the passage through the hopper the moisture content (Flosdorf-Webster method) [20] remains 1.0 to 2.0 per cent, thus providing for flash solubility. The product can be made to dissolve with ease in 1.5 to 2.0 minutes' time. The hemoglobin content is inconsequential, varying from 80 to 300 mg. per cent in the four times concentrate.[21] The fibrinogen content is so low as to be almost negligible and the pH is elevated to about 8.4.[16b]

In the routine service we have dispensed three different quantities of desiccated plasma containing 6.25 gm., 12.5 gm. and 25 gm. of the dry product. These provide for 25 c.c., 50 c.c., and 100 c.c. of hypertonic (four times concentrated) plasma respectively. Approximately 10 per cent of the final volume is deleted in estimating the amount of water added in order to allow for the solids. Thus for 100 c.c. of four times concentrated plasma 90 c.c. of water are added to 25 gm. of solids. It must be mentioned that four times concentrated here is concerned with citrated plasma and not unmodified plasma. Thus the protein content averages 20 gm. per cent.

We have experienced no difficulty in handling this product in syringes as mentioned by others.[3f] When rushed for time the product can be dissolved and given to a patient in shock in less than three minutes.

Indications and Contraindications

The variety of cases seen in a routine service serves as a good means of testing the indications and encountering the contraindications.

Indications for Intravenous use of Hypertonic (4 × Concentrated) Plasma

I. Shock—rapid building of blood volume and acceleration of circulation. Excellent response in all forms of shock:

A. Traumatic.
B. Post-hemorrhagic.
C. Shock of burns.
D. Neurogenic.
E. Incompatible blood transfusion.

II. Control of Plasma Protein Level—rapid filling of protein stores, elevation, and sustainment of plasma protein level:

A. Hypoproteinemic states

1. Protein depletion after gastrointestinal operation, fistulae, starvation.
2. Liver damage.
3. Massive exudation—pneumonia, exudates in serous cavities, late phase of burns, large ulcerations.
4. Protein loss—through kidney (nephrosis), gastrointestinal tract (ulcerative colitis).

B. Intravenous protein feeding when food by mouth restricted.

III. Control of Fluid Balance—prolonged and powerful osmotic effects in edemas:

A. Edema.

1. General: severe hypoproteinemic states and after excessive intravenous saline.
2. Local:

a. Pulmonary (preliminary bleeding to prevent increased blood volume must be done).
b. Cerebral—head injury, brain surgery, eclampsia.

B. Excessive fluid and protein loss—infectious diarrhea, cholera, dysentery (together with other fluids in combating hypovolemia and hemoconcentration).

IV. To Provide Antibodies in Infectious Disease:

A. Directly—convalescent plasma.
B. Indirectly—to maintain body protein stores at levels necessary for effective antibody formation.

The outline of indications for the clinical use of concentrated plasma is self-explanatory. The evidences supporting the use of hypertonic plasma in shock, regardless of its cause, are given below. In burns, the enormous quantities of protein lost may be rapidly replenished gram for gram by this means. In moderate or profound hypoproteinemic states the protein stores and plasma protein level may be successfully restored by means of repeated large doses. Here fluid administration is frequently not essential and the concentrated product affords the best means of giving large doses intravenously. In patients who are unable to take food by mouth, as following gastrointestinal operations, a normal nitrogen balance can be maintained.[22, 12] The giving of glucose and vitamins alone makes for an unbalanced metabolism. In edemas the increased osmotic forces help in shifting fluids from ab-

normal locations. In severe cases of pulmonary edema which are refractory to bleeding alone, the addition of concentrated plasma is of value. Here one must insure against overloading the heart by adequate preliminary bleeding. Even in severe dehydration its judicious use following other fluids may be of help. Here it acts in a manner comparable with glucose [23] by pulling in fluids given subcutaneously and encouraging an adequate renal plasma flow. Convalescent serum or plasma administered by this means may be given in greater doses, more rapidly and with less discomfort to the patient than by any other method.

There are very few contraindications to the use of concentrated plasma and this form of plasma properly prepared is innocuous. The major contraindication is the presence of incapacitating myocardial damage. In congestive heart failure the additional and sudden increase in blood volume may be dangerous. Hypertension by itself, however, is not a contraindication. Patients with a blood pressure of 200 systolic and 110 to 120 diastolic have been given substantial doses (100 to 150 c.c.) of four times concentrated plasma on many occasions without harmful results. Dehydration approaching the critical level of 10 per cent of the body weight [24] is obviously a contraindication. Even here concentrated plasma may be used in mobilizing fluids if the latter are given subcutaneously.

Clinical Data

The present report relates further clinical experience with desiccated plasma, summarizing the clinical results from the inception of the routine service at Baylor University Hospital to the present time. Of necessity it overlaps with previous reports.[8a, b, c, d]

Almost 1,000,000 c.c. of blood have been converted into plasma and desiccated by the adtevac process. Seventy-three thousand two hundred and thirty-seven c.c. (73,237 c.c.) have been given clinically under controlled conditions, 50,107 c.c. to patients in Baylor Hospital and 23,130 c.c. to

Table I

	No. Cases	Smallest Total Dose 4 × Conc. Plasma c.c.	Largest Total Dose 4 × Conc. Plasma c.c.
Shock Prevention	34	50	250
Burns	9	100	1200
Protein Feeding	31	50	7690
Edemas	7	50	620
Head Injuries and Neurosurgery	32	50	300
Toxemias of Pregnancy	28	50	370
Miscellaneous	48	20	150
Total	189*	Av. 53	Av. 151

* Six cases included in two groups.
Note: Total dose includes one to several injections.

patients on the outside. The former figure is related to 276 cases that have received a total of 674 doses of four times concentrated plasma. There have been only five febrile reactions, all of pyrogenic type, making a reaction rate of 0.74 per cent.

The cases have been separated into groups in order to emphasize the importance of the introduction of large amounts of protein intravenously. The major groups, besides the shock group, are listed in table 1.

Shock

It is accepted that the shock syndrome results from a disparity between the circulating blood volume and the vascular capacity, due mainly to an actual decrease in blood volume.[25] Sooner or later the associated anoxemia, with its increased capillary permeability and seepage of plasma into the tissue spaces tends to progressively accentuate this disparity. The main purpose of shock therapy is to restore the effective or circulating blood volume as rapidly as possible, thus breaking the anoxemic cycle. The disagreements regarding the pathogenesis of shock [26] do not invalidate this aim.

The depleted blood volume may be due to a loss of red blood cells and plasma (whole blood) or to a loss of plasma alone. In most instances the red blood cell loss, even if great, is relatively insignificant and only in rare cases does it influence the subsequent course.[27, 5b, d, e, 4, 2d, e] In Amberson's experiments [27b] animals appeared normal when their blood was replaced by a 12 to 14 per cent solution of free hemoglobin. Death by asphyxia occurred only when the hemoglobin content was reduced to a 3 per cent concentration.

Various solutions have been used to replenish the depleted blood volume. The evanescent and frequently ineffective results obtained with intravenous saline and glucose solutions whether in isotonic or hypertonic form, have been aptly stressed.[28, 26a, e, b; 5a, b, e, f, g; 4, 2i] These solutions may hydrate tissues to the point of producing edema but most often they fail to maintain the blood volume. Furthermore, plasma proteins may be washed out of the blood stream by their use in cases with capillary damage.[5f] Other solutions as 6 per cent gum acacia, Ringer hemoglobin and gelatine-saline solutions have proved unsatisfactory. Although whole blood transfusions, within certain limits, are effective, the relative insignificance of the added red cells plus technical difficulties makes this procedure lose a great deal of its former value. Only in rare cases of extremely severe red cell depletion, losses approaching three-fourths to four-fifths of the circulating hemoglobin content,[27a] are blood transfusions absolutely essential. On the other hand, the importance of plasma proteins in maintaining blood volume and combating shock meets general agreement. Therefore, in shock therapy the basic problem is one of deciding which type of protein containing fluid is most effective.

There is evidence that dilute or half-strength plasma suffers from deficiencies comparable to those of saline and glucose solutions, for the crystal-

loid containing portions of these solutions are lost to the tissues.[21] The possible effectiveness of this procedure is not denied but it does not constitute the ideal treatment. It perhaps has its greatest value in most severe grades of dehydration.

The ideal treatment, consequently, rests between normal (isotonic) and concentrated (hypertonic) plasma. The researches of several have emphasized the value of normal plasma infusions.[2a, b, c, d, e] That this is an effective means of combating shock is well agreed. But, is it the most effective treatment?

Blalock and associates have shown that with widespread capillary damage large amounts of plasma and its proteins may be lost from the blood stream. This loss may continue at a rapid rate in spite of continuous intravenous administrations of plasma. It is also stressed that colloid should be given " fast enough to increase the level in the blood to the point of retaining an effective circulating volume in spite of the losses that may occur." [15d] There are obvious clinical implications of these deductions. Normal or isotonic plasma may completely control shock or it may maintain circulating blood volume by enormous and multiple infusions sufficient to combat severe grades of shock. However, it serves mainly as a substitution and it does not tend to reverse the abnormal physiologic mechanisms of shock. Its normal isotonic osmotic properties make it as subject to seepage through the capillaries as the patient's own plasma. On the other hand, concentrated plasma actually tends to reverse the known mechanism of shock. It increases blood volume rapidly by withdrawing fluid from the tissues and its hypertonicity affords stimulating effects on the capillaries.[29, 28c] This is illustrated clinically by the rapid changes in the patient. The blood pressure response in a large majority of the patients is sudden, the pulse becomes more regular and there is obvious clinical improvement. Given rapidly and in sufficient quantities its action is quicker than that of other agents. In addition any degree of protein depletion through damaged capillaries, however great, can be coped with by rapid administration of large doses of protein. This appears to approach an ideal shock treatment.

In connection with the use of hypertonic solutions harmful dehydration is frequently discussed. Most cases of hematogenic shock, particularly in a general hospital, are sufficiently hydrated to be capable of easily supplying interstitial water to dilute 100 to 500 c.c. of four times concentrated plasma. Such fluid can be rapidly and effectively substituted by hypodermoclysis. By this means the risks of intravenous saline are averted. For military emergencies the subcutaneous saline is less apt to cause pyrogenic reactions thus facilitating its preparation. In this same regard the approximately 3 per cent sodium chloride concentration of the plasma is of value. The hypertonic effect of this fraction is soon lost, but it serves to hold water that is given orally or parenterally in the body, and at the same time, it discourages potassium imbalance.[30]

TABLE II

Degree of Shock	No. of Cases	Aver. Dose c.c.	Results			
			Excellent	Good	Transient	Poor
Severe	45	183	26	3	11	5
Moderate	35	129	30	5		
Mild	13	82	12	1		
Total	93	131.3	68	9	11	5

CONTINUATION OF TABLE II

Degree of Shock	No. of Cases	Time Interval Before Blood Pressure Above Critical Level									
		5–15 Min.		15–45 Min.		45–60 Min.		Over 60		Not at all	
		No.	%	No.	%	No.	%	No.	%	No.	%
Severe	45	18	40	10	22.2	6	13.3	6	13.3	5	11.1
Moderate	35	23	65.7	7	20			5	14		
Mild	13	9	69.2	2	15.4	2	15.4				
Total	93	50	53.76	19	20.43	8	8.6	11	11.8	5	5.36

EXPLANATION OF TERMS IN TABLE II

I. Degree of Shock: arbitrary clinical evaluation as follows:

A. Grade of Shock
1. Severe: signs of peripheral circulatory failure plus imperceptible or near imperceptible pulse or blood pressure, or coma.
2. Moderate: blood pressure below critical level (80/40) and between 50 to 75 systolic and 0 to 50 diastolic and signs of peripheral circulatory failure.
3. Mild: Blood pressure near critical level and signs of peripheral circulatory failure.

B. Grade of Response
1. Excellent: Sudden response of blood pressure, above critical level in 15 to 45 minutes, with clinical improvement.
2. Good: Slower blood pressure response, 45 minutes to 1.5 hours to reach 80/40 or above.
3. Transient: Elevation of blood pressure above critical level and gradual drop to death.
4. Poor: Blood pressure not elevated to critical level, death.

Table 2 summarizes the shock cases. This classification on a clinical basis, although not ideal, is the only means of appraisal at the present time. The rapidity of action of concentrated plasma is well emphasized.

Ninety-three cases of shock have been studied thus far. All have had clinical signs of peripheral circulatory failure, that is, weak pulse with tachycardia, cold and pale skin, sweating, restlessness, mental confusion or coma, plus a depression of blood pressure. In 77 of the cases (82.8 per cent) the blood pressure was below the critical level taken as 80 mm. Hg systolic and 40 mm. diastolic. There were 45 cases (48.4 per cent) who received no other intravenous fluids until shock was well controlled and the blood pressure was well above the critical level; 48 cases (51.6 per cent) had both four times concentrated plasma and other intravenous fluids spaced at

shorter intervals. In all cases that responded, the response was directly related to the administration of the concentrated plasma. Only five cases or 5.36 per cent failed to respond.

In 66 cases (70.9 per cent) hemorrhage played a part in the blood volume depletion. Fifty-four cases (58 per cent) had surgical operations before treatment.

Doses

The dose in shock depends strictly on the response. One hundred c.c. of four times concentrated plasma may be given as the initial dose to be followed by as frequent similar doses as are needed to control shock. One hundred c.c. may be given intravenously as rapidly as possible through a 19 gauge needle, taking usually one to two minutes' time. The doses have been given at this speed on numerous occasions. On one occasion it was necessary to administer 600 c.c. of four times concentrated plasma over a period of a few hours to control shock. Often 100 to 200 c.c. are sufficient.

Shock Prevention

This group consists of 34 cases in whom it was considered shock might develop. These doses were administered following accidents, preoperatively and postoperatively. Shock did not develop in any case in this group but it becomes difficult to link this directly to the administration of hypertonic plasma in each case. The prevention of shock is a promising field.

Burns

Concerning burn cases, particularly severer grades, many have emphasized the need for maintaining the circulating plasma protein [31, 15a, c, 1c] level. In this regard maximum therapeutic efficiency during the period of protein loss can be attained by a combination of normal and hypertonic plasma therapy. In a case with almost total body surface burn following an oil explosion, hemoconcentration was more effectively controlled when concentrated plasma was given along with normal plasma. This case passed the shock period successfully to die three weeks later of pneumonia. Another case with three-fifths body surface burn also passed the shock period successfully but died suddenly one week later. During the first four days this patient received 6,580 c.c. of normal plasma, 1,100 c.c. of four times concentrated and 100 c.c. of three times concentrated plasma plus 2,500 c.c. of 5 per cent glucose and saline given very slowly to keep the vein open. Hemoconcentration and the plasma protein level were completely controlled only by this means. On the fifth day a blood volume estimation with Evan's blue dye revealed a normal plasma volume (4,610 c.c.) with an absolute plasma protein content of 274 gm. The estimated weight of this patient was 90 kilograms.

In the burn group one case received normal plasma alone. In this instance 3,000 c.c. during the first 36 hours were sufficient to combat shock.

The other cases received hypertonic plasma along with normal plasma. It was felt that the absolute plasma protein content as well as the protein concentration could be more effectively maintained, particularly in burns involving over one-third the body surface, by this combination therapy.

Protein Feeding

Surgical patients for the most part receive adequate carbohydrates, crystalloids and vitamins but frequently the protein metabolism is neglected. This is particularly true of patients who have been on a semi-starvation diet due to their illness, and following gastrointestinal operations.

It has been well demonstrated that plasma proteins are utilized by body tissues.[12] Recently a case of congenital megacolon and jejunal fistula was kept in nitrogen balance by this means. This patient received 7,690 c.c. of four times concentrated plasma for this purpose in a total of 100 doses plus 5,000 c.c. of normal plasma during 43 days. If one wishes to administer 100 gm. of protein intravenously to a patient in 24 hours, 50 c.c. of four times concentrated plasma could easily be given at intervals throughout the day. This could be accomplished in a total time of 20 minutes whereas a comparable amount of normal plasma (2,000 c.c. citrated plasma) would necessitate one to three hours at the least.

In the 31 cases given concentrated plasma for this purpose benefit was noticed in several. The others received small quantities making evaluation difficult.

Edemas

Nutritional edema, saline edema, nephrotic edema and cerebral edema are all benefited. Two cases with nephrotic syndrome gave disappointing results in spite of large doses. One was a chronic case, the other had glomerular damage. Failure of response in similar cases has been reported.[15g, h]

Head Injuries and Neurosurgical Operations

That concentrated plasma is capable of reducing increased intracranial pressure was first demonstrated in 1938.[3e] The effect is greater and more prolonged than that of concentrated glucose. Harmful dehydration as discussed [32] has not been observed.

Most of the cases in this group were surgical. The effects on intracranial pressure were not observed by manometric studies making evaluation difficult. There were no harmful results and several cases were benefited.

Toxemias of Pregnancy

The study of 28 cases, including 12 cases of eclampsia and 16 of preeclampsia, has failed to show the good results expected from preliminary observations. Transient benefit was noted in several cases but a sustained control of blood pressure level was not accomplished. The diastolic level

of blood pressure is less affected. In the few favorable results mixed treatment obscured the results.

Reactions

Properly prepared desiccated plasma is innocuous as shown by the febrile reaction rate of 0.74 per cent, five reactions in 674 doses. Urticarial reactions are rare. Other minor discomforts include slight dull ache along the vein which can be controlled by slower administration and transient backache in parturient women seldom lasting more than five minutes. Shock patients with a full stomach have been observed to vomit once shortly after the injection. These are usually comatose patients. Two transient tetanic carpopedal spasms in children have been previously mentioned.[3e]

Comment

It can now be stated that desiccated plasma can be produced safely by bulk desiccation. Furthermore, a partially open method, which is absolutely necessary for mass production, carried out in properly air-conditioned rooms by aseptic conscientious workers has been proved to be safe by extensive experience. The original objections [17a] to this process have been overcome as proved by bacteriological and moisture content studies and the giving of 75,000 c.c. of hypertonic (four times concentrated) plasma clinically. The febrile reaction rate of 0.74 per cent speaks for itself.

At the present time others [33] have certain objections to the product in its present form in spite of the very favorable clinical trial. The proper consideration of pyrogens [34] is absolutely essential in appraising any reaction rate. The relatively few milligrams of hemoglobin in this plasma have no bearing on reactions, as proved by others.[35] We have given, on occasions, large amounts of hemoglobin in the plasma without harmful results. Bacteriological checks of all phases of this method have given negative cultures repeatedly. Contamination reactions [2e] have not been observed. The potassium content is not harmfully increased. The low moisture content encourages rapid solution.

In this communication we have purposely disregarded distinctions between plasma and serum as a therapeutic agent. The proper preparation of either gives an innocuous product. Adtevac plasma, prepared as outlined, is literally neither plasma nor serum. The use of Filter cel during Seitz filtration removes most of the fibrinogen fraction leaving a plasma that approaches serum in composition. It has been suggested that this material be called a partially defibrinated plasma.[36] Such a product does not produce reactions.

Hypertonic plasma offers two therapeutic weapons, first, a direct means of substantially increasing intracapillary osmotic forces, and second, a simple and effective manner of introducing large amounts of protein intravenously. These two points are of great importance in any pathological state associated with an appreciable decrease in absolute or circulating plasma protein content. This is true regardless of the cause of the protein depletion, whether

due to an inadequate intake of protein foods, decreased production of proteins, depletion of protein stores or due to loss through large capillary beds, kidneys, or wide ulcerative surfaces. With concentrated plasma any degree of clinical plasma protein loss can be coped with.

In shock these two features are of prime importance. The rapid increase in blood volume has been previously demonstrated [3c] by the immediate and sustained dilution of hemoglobin, a drop in venous whole blood specific gravity and a lowering of the hematocrit reading. At the same time the plasma specific gravity remains about the same, meaning that the concentration of protein remains unchanged and may be increased. There are possible stimulating effects on small sized vessels and capillaries. The withdrawal of misplaced fluids places capillary and tissue function on a more normal basis. These features tend to reverse the abnormal physiologic mechanism of shock and account for the rapid clinical responses.

Following copious hemorrhages and prior to the establishment of widespread capillary damage, it has been illustrated [37, 28b] that the lowered capillary hydrostatic pressure encourages an inrush of interstitial fluid as a means of supporting the diminished blood volume. The success of this mechanism may prevent the development of post-hemorrhagic shock. If this mechanism fails, capillary damage occurs and the diminished blood volume is accentuated by seepage of plasma through the capillary walls. To be effective, intravenous saline solutions must be given before capillary damage develops or else unnecessary risks are taken. In this interval hypertonic plasma enhances an established physiologic mechanism and may prevent the development of post-hemorrhagic shock. In this regard the unfavorable observations of Black and Smith [38] are not supported by others. If capillary damage ensues then hypertonic plasma continues to be effective as in other types of shock.

Gamble [39] has pointed out that the large volume of interstitial fluid (15 per cent of body weight) provides a strong and prolonged defense for the blood plasma volume. In rigid dehydration experiments a period of 10 days with continuous withdrawal of sodium and depletion of the interstitial fluid was necessary to produce severe harmful effects. During this period the plasma volume was maintained at the expense of the interstitial fluid. By giving these findings a clinical meaning one can discern that the transient withdrawal in shock of a comparatively small volume of interstitial fluid cannot be deleterious. Of greater value is the fact that the more important of the two components of extracellular body fluid (plasma) is being sustained through a critical period. The kidneys being in a depressed state of activity this fluid is not readily lost from the body and it can be rapidly replenished later.

Recent objections [2e] to the use of hypertonic plasma in shock lack support. It is known that the blood volume is rapidly increased following the giving of this substance.[40, 3e] Certain British workers [3f] have observed that 80 per cent of the blood pressure elevation occurs in the few minutes follow-

ing the administration of concentrated plasma. It has never been denied that normal plasma is effective in shock treatment, but we believe that it does not appear to be the most effective therapy available at the present time.

The main emphasis in this report has been on restoring the circulating blood volume because this is the most important feature of shock therapy. Other procedures, such as prevention of exposure, warm surroundings, the giving of oxygen, etc., are of additional value.

In military medicine one of the greatest problems is shock. In this regard, the need for a therapeutic agent of high efficiency coupled with ideal storage properties is essential. In shock such an agent appears to be available in properly desiccated plasma. Drying machines that are capable of successfully supporting a routine service in a 400 bed hospital are capable of expansion to meet any demands. For mass production, bulk desiccation, first mentioned by Elser,[16b] is safe and can be easily performed.[3a, b, c, d]

Conclusions

1. Bulk separation and desiccation of plasma or serum with proper precautions is a safe procedure.
2. Bulk desiccation is essential for mass production of desiccated plasma.
3. Desiccated plasma prepared by the adtevac process as outlined is innocuous.
4. Hypertonic plasma (four times concentrated) is highly effective in combating hematogenic shock and seems to reverse the abnormal physiologic mechanism of shock.
5. Harmful dehydration of hypertonic plasma during a short interval of time appears to have been over emphasized.
6. With hypertonic plasma any degree of clinical plasma protein loss can be controlled.
7. Hypertonic plasma is the most efficient agent available at the present time for increasing intracapillary osmotic forces.

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OBSERVATIONS ON THE SPECIFIC TREATMENT (TYPE A ANTISERUM) OF STAPHYLOCOCCAL SEPTICEMIA; SECOND REPORT*

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IN an earlier communication [1] published in this journal, a preliminary account was given of the experimental treatment of staphylococcal septicemia with specific antibacterial serum. Obtained from rabbits following immunization with intact, formalinized organisms, the antiserum was particularly prepared to contain high titers of antibody capable of reacting with the somatic carbohydrate extractable from pathogenic (Type A) staphylococci.[2] The rationale for the therapeutic expectancy of such an antiserum was based on the theoretical considerations arising from the observation that precipitins for the carbohydrate in question are demonstrable in the sera of those patients only who have recovered from severe, generalized infection.[3] Although it was obviously impossible to arrive at an appraisal of the antiserum in the preliminary report, the results were sufficiently encouraging to warrant a more extended study on the therapeutic effectiveness of the Type A, anticarbohydrate serum. This has now been done, since in the interim 98 unselected patients with genuine staphylococcal septicemia and four with severe infection and unverified septicemia have received the serum as the basic treatment during their courses of infection. While it may be argued that even this number perhaps fails to supply the statistical basis eventually desired, it is nevertheless true that the series is now large enough to establish the principles involved and to suggest at least a potential value for such an antiserum.

METHODS OF STUDY

Type A Antiserum. The antisera under study were all prepared in rabbits, originally in this laboratory as described elsewhere,[1] for use in the first 32 patients. Later, both the Lederle Laboratories of Pearl River, N. Y., and the Eli Lilly Co., of Indianapolis, furnished sera prepared and standardized under the writer's direction, and more recently, in fact, the former organization not only incorporated certain modifications in production, but has since evolved purified and concentrated preparations. It may be said at this point, however, that in so far as anticarbohydrate titer and therapeutic efficiency are concerned, each of the three laboratories prepared successful antisera.

Selection of Patients. No attempt has been made to select patients. Calls for serum were answered by priority irrespective of the patient's age, clinical condition or complication, duration of the infection, prognosis, etc.

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The only restriction imposed was that each patient must have had at least two positive blood cultures on consecutive days before administration of serum. Further details concerning the patients studied, however, will be discussed more appropriately later in this report.

Administration of Antiserum. Before giving serum in therapeutic doses, it was necessary to test each patient's sensitivity to the serum. This was accomplished by determining the effect of the serum on blood pressure, pulse rate, and respiration. A mixture of 1 c.c. of serum in 10 c.c. of saline was injected slowly by the intravenous route, and the patient was watched over a period of about one hour. If within that time no significant changes occurred in blood pressure (reduction of 15 mm. or more), pulse rate (increase of 15 beats or more per minute), or respiration, serum treatment was then started. It may be said at this point that in no individual was this test in the least harmful. In each case it was possible to start serum in therapeutic doses, although in several because of various reactions (urticaria, respiratory difficulty, increased pulse rate, etc.) the administration had to be interrupted and either continued intravenously later, or from then on only by the intramuscular route. In the latter case, 10 to 20 c.c. of serum were repeated at intervals of four to six hours. In the end, the route of administration apparently played no important part; obviously more time is required to raise the antibody blood level to an effective point by the intramuscular route, but having once been reached, antibody concentration may readily be maintained by this method.

Determining the initial quantity of antiserum to be administered has been a difficult matter, because several factors, some definitely obscure, enter into the dosage. Since the infection, not the age nor sex of the patient, is to be combated, an attempt has been made to estimate the dosage of serum according to the degree of infection. Thus, the number of staphylococci per c.c. of blood, duration of infection, rapidity of spread, distribution and extent of metastases were all considered. Consequently, the initial dosage was varied from 60 c.c to 120 c.c. of serum. As will be described, this was frequently followed by further administration on successive days as deemed necessary.

In giving the serum, it was always diluted at least once with saline, Hartmann solution, or Ringer's solution. The mixture was introduced slowly by gravity and if untoward symptoms developed, the injection was immediately stopped and adrenalin was used, sometimes supplemented by caffeine or some other stimulant.

Index of Adequate Serum Therapy. In order to determine when sufficient serum had been given, skin tests were performed with the carbohydrates derived from staphylococci. That from Type A was used for the actual test and that from Type B (non-pathogenic) for purposes of control. The carbohydrates were used in dilutions of 1 : 100,000 of which 0.2 c.c. was injected intracutaneously. A positive reaction manifested itself within a few

minutes by a wheal and erythema, as described in the earlier report. Thus, the appearance of such a reaction was interpreted as indicating an excess of antibody in circulation and, therefore, that further administration of serum would be superfluous. Granted that in some individuals with highly reactive skins, reactions may be difficult to interpret because of their nonspecificity, such examples, nevertheless, are decidedly in the minority and it may be said that in every case exhibiting a genuine reaction to Type A carbohydrate, recovery inevitably followed.

The following routine was, therefore, adopted in performing skin reactions. Skin tests were done on each day of serum treatment including the first day. Preferably 20 to 24 hours should have elapsed since administration of serum before injecting carbohydrates. This is an important precaution because it has been found that immediately following introduction of serum the skin reacts avidly with homologous carbohydrate, in some instances within an hour to an hour and a half following cessation of serum. This is more often than not, however, merely a transient reactivity to be dissipated completely by the following morning. If, then, after about 24 hours the skin test elicits a strong reaction, serum therapy is discontinued, while lack of any reaction or even a moderate reaction implies that more serum should be given. Again the dosage is arrived at by several considerations, but in general 40 to 60 c.c. make an average quantity. The procedure of daily skin test and additional serum is thus continued until the development of a strongly positive reaction.

If skin reactivity to Type A carbohydrate cannot be determined, because carbohydrates are not available, or because of lack of experience with the vagaries of skin reactions, a less accurate, but more or less satisfactory index of further serum administration may be deduced from the patient's general condition, the temperature chart, and the blood culture. To accelerate results in the last case, it is recommended that blood be cultured directly in agar plates, since with clinical improvement growth in broth may be delayed as long as three and four days.

Supportive Treatment. All the patients in this group received whatever supplementary treatment was indicated. Thus, transfusions were given when the red blood count fell to 3,500,000 cells per cu. mm. Surgical care was considered of utmost importance and, as far as the writer is concerned, on a par with serum therapy itself. It must be remembered that staphylococci not only cause localized abscesses, but possess a considerable capacity for tissue destruction, eventuating in replacement with scar tissue. Consequently, unless the abscess is forced to evacuate outwardly, it may well discharge inwardly, thus frequently reaching the circulation. Moreover, unless adequate drainage is established all those toxic by-products liberated by the destroyed tissues can be eliminated only by absorption, obviously adding to the general toxemia, even assuming that the bacteria themselves have been effectively suppressed. It is, in fact, the opinion of the writer that staphylo-

coccal septicemia is as much a surgical as a medical emergency, and for effective management the condition requires complete collaboration of surgeon and internist or pediatrician.

What surgical procedures were to be adopted in this study were left for the surgeon in charge to decide. In a general way, however, it seemed wiser not to intervene in the spreading cellulitis or edematous type of infection and to delay operative procedures until the lesion began to localize, whether the lesion was of the bony or soft tissues. It is realized, of course, that opinion is divided on the proper course in such cases, so that it may be dangerous to dogmatize. The impression has been gained in this study that the use of serum before operation, particularly in cases of osteomyelitis, is a prophylactic measure of value, and for this reason this procedure was frequently adopted in later patients.

At this point it may be well to add that where sulfonamides had been part of the treatment before serum was used, the drugs were promptly withdrawn. It was discovered later, however, that in certain cases the drugs were continued, but such instances formed a very small minority, and it is felt that the infection was not materially influenced by the additional treatment.

Collateral Bacteriological Studies. During the course of treatment daily blood cultures were made, in most cases by plating 1.0 c.c. and 2.0 c.c. of blood and by inoculating broth with 5.0 c.c. or more of blood. The plates were incubated, in general, for 48 hours before making final estimation of the number of colonies per c.c. of blood, while the broth cultures were incubated for one week before being discarded as sterile. In certain infrequent instances, however, it was not possible to carry through this procedure. Where drainage was instituted, cultures of the escaping pus were made on infusion blood agar plates so that the strains from the localized lesions might eventually be compared with those originating from the blood. Each strain was tested for its ability to ferment mannite, since typical pathogenic cultures produce acid in this sugar,[4] and the organism was subsequently classified by the carbohydrate extracted from it. In addition, each strain was measured for virulence in white mice, and more than half were tested in rabbits as well. Random strains were also inoculated in guinea pigs.

Analysis of the bacteriological information reveals that practically each patient had at least three daily positive blood cultures before the administration of serum. As will be shown later (table 4) there were four exceptions to this rule.

Variations in the numerical count of colonies covered a range of several thousand colonies per c.c. of blood, as will be brought out later. Every strain tested fermented mannite; in an occasional culture, however, fermentation was delayed to the third or even fourth day. In each case Type A carbohydrate was extracted from the bacterial cell. Comparison of the strains from localized pus and blood cultures disclosed no variations in the

tests conducted, suggesting, therefore, that the organism in the blood had actually penetrated from the external focus.

Tests for virulence in the different animals were highly disappointing, since it was hoped that an animal-virulent strain would sooner or later be encountered. Death was induced only by excessively large numbers of organisms and the results were extremely irregular. Thus, some cultures killed white mice in dosages of 0.1 c.c. (*ca.* 50 million organisms) and rarely 0.01 c.c. (*ca.* 5 million organisms) of young broth cultures injected intraperitoneally or intravenously, but the results could not be duplicated with any degree of regularity. Many cultures, even in dosages of 0.5 c.c. or 1.0 c.c., had little effect on any of the three animals (mouse, rabbit, guinea pig). If it is recalled that the organism tends toward the classical formation of clusters, it will be realized that when death does occur following the injection of large dosages, the fatality may be as much the result of capillary emboli as of actual infection. In any case, it is extremely difficult to measure in the commoner animals the virulence of strains derived from man, even when the infection is fatal.

Clinical Observations

As stated earlier, 102 patients have now been treated with antistaphylococcal, Type A rabbit serum. This number represents a great variety of disease, with patients ranging in age from four months to 72 years. The largest group was composed of cases with acute osteomyelitis complicated with septicemia, there being a total of 26 such examples. The next largest group included cases with heart involvement (15 with endocarditis and three with pericarditis) and a third group of nearly the same size was made up of cases of furunculosis (14 cases). The other individuals represented a scattering of clinical conditions as the predominant factor in the infection, such as primary pneumonia in eight, sinus thrombosis and meningitis in three, septicemia following abortion in three, etc, etc. In other patients the staphylococcal septicemia was aggravated by diabetes (difficult to control in five); sulfanilamide poisoning with severe leukopenia in two; congenital jaundice in two; tuberculosis of the spine and dissecting aneurysm in one; pemphigus foliaceous in one; leukemia in one; malnutrition (in an infant), one; Cushing's syndrome, one; arsphenamine poisoning with extensive hepatic damage in one; nephrosis, one; and internal hemorrhage due to an injury in one. Of the total series, 62 were treated in St. Louis, 18 in various places throughout the country, and 22 at the Philadelphia General Hospital. The third group is being published separately from that institution [5] but will be reviewed summarily here to render the analysis as complete as possible.

Of the 102 patients treated as described, 48 survived and 54 died. In order to present the data simply and comprehensively, it is proposed to submit a separate analysis of the fatal and non-fatal cases.

Synopsis of Patients Recovering

Before entering upon a description of the individuals considered as successfully treated with Type A serum, it may be relevant to illustrate by clinical observation the specificity of the antistaphylococcal serum.

Case Report

Case 83. A white female, 34 years of age, entered the hospital with extensive pemphigus foliaceous of three months' duration. After six weeks' hospitalization during which the skin condition became intensified rather than diminished, the patient developed a septic temperature which was soon proved to be due to a septicemia caused by hemolytic *Staphylococcus aureus* of the mannite-fermenting, Type A variety. The first three daily blood cultures were pure growths of staphylococcus,

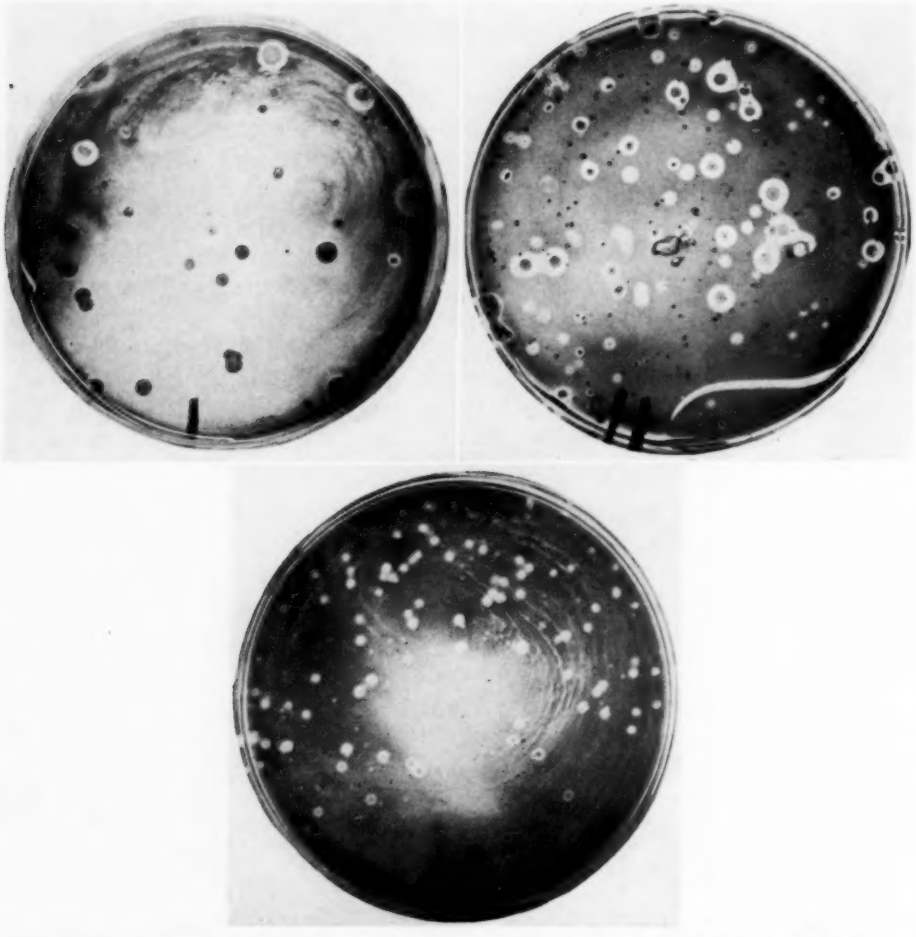

Plate 1. Specificity of Type A Antiserum. Photographs of blood culture plates made on first, fourth, and seventh days of septicemia. Upper left, pure staphylococci; upper right, staphylococci and streptococci; lower, staphylococci eliminated—pure culture of streptococci remains (*vid.* text).

but on the fourth day, with the number of colonies of this organism definitely receding, the plates were noticed to contain several colonies of hemolytic streptococci. Administration of serum which had been started on the second day was accompanied by a complete disappearance of the staphylococci by the fifth day of septicemia (third day of treatment), while in the same period the number of streptococcal colonies distinctly increased. From then on the blood stream remained free of staphylococci. The patient was given sulfanilamide in large doses in an effort to check the streptococcus invasion but without avail. The blood culture was consistently positive for this organism for some two weeks; towards the end, in fact, the cultures showed mixed growths with diphtheroids and colon bacilli which were probably due to the technical difficulty of obtaining uncontaminated blood, because of the condition of the skin. At postmortem examination, no metastatic abscesses were detected, and a vegetative endocarditis on the tricuspid valve yielded a pure growth of streptococci. This is considered a remarkable example of the specificity of the antiserum, further evidence of which has been obtained experimentally and will be presented at a future date. In order to illustrate the forerunning observations, photographs (plate 1) are given of three blood cultures obtained on the first, fourth, and seventh days of septicemia.

The patients represented among the recoveries were well distributed as to age and clinical manifestation. The ages varied from 18 months to 56 years and the primary foci divided themselves as will be seen in table 1, as follows: osteomyelitis, 24; furunculosis, seven; primary pneumonia, four; localized abscess following trauma, two; infected blister of heel, two; infected pimple of face, two; self-induced abortion, two; undetermined, one; meningitis, three; and frontal sinusitis with osteomyelitis, one.

TABLE I

Summary of Patients Surviving Classified by Initial Infection

Total number of patients treated	102
Total number of patients surviving	48
Osteomyelitis *	24
Furunculosis	7
Pneumonia †	4
Localized abscess following trauma	2
Infected blister of heel	2
Infected pimple of face	2
Endometritis (self-induced abortion)	2
Undetermined	1
Primary meningitis	3
Frontal sinusitis with osteomyelitis	1
Total	48

* The evidence suggests that three patients with pneumonia and one with osteomyelitis did not have septicemia.

† In addition to the primary pneumonias listed, there were 10 examples of metastatic pulmonary infection.

It should be stated in this connection that one of the patients with osteomyelitis had a transient bacteremia rather than septicemia; and of the four patients with pneumonia only one can be certified as having septicemia. In addition to septicemia there were numerous other metastatic complications as

pneumonitis or lung abscesses in 10, with pleurisy or empyema in four of these cases; abscesses of the kidney, four; panophthalmitis, three; iritis with hypopyon, one; sulfanilamide poisoning with agranulocytic leukopenia (white cell count, 800), one, etc. Of the 24 cases of osteomyelitis it was felt that nine had no metastatic spread of infection. Thus, it is seen that as far as is possible the distribution of patients is typical of staphylococcal septicemia with perhaps a larger than average share of osteomyelitis.

Effect of Antiserum on Temperature. It may be of interest to describe the effect of the antiserum on the patient's temperature. The dramatic drop in fever associated with crisis was observed only rarely. In three cases the temperature actually fell to normal overnight and remained close to that point until complete recovery. In two of the three patients, the temperature subsequently arose again. In one case this occurred after seven days, the fever of 2° F. being due to a panophthalmitis which was present early during the septicemia. With enucleation, the temperature promptly fell to normal and remained so throughout the patient's stay in the hospital. In the second instance, a rise of about 2.5° F. was associated with pleurisy with effusion. After paracentesis the fever disappeared and the effusion did not recur.

As illustrative of this type of effect of serum therapy on fever a summary of case 42 is here cited and the temperature chart reproduced (figure 1).

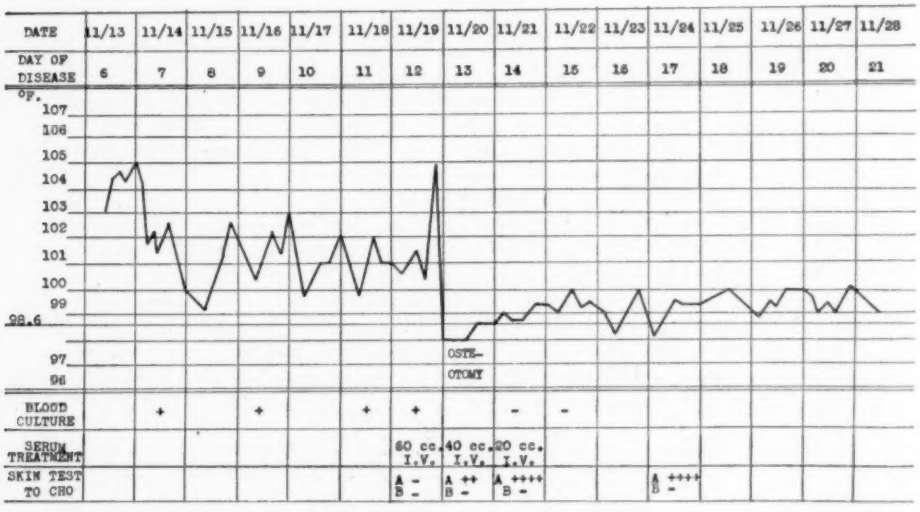

FIG. 1. Effect of Antiserum on Temperature. A. Fall by Crisis. In this and succeeding charts minus signs represent test performed was negative, while plus signs indicate an arbitrary degree of positiveness. The numerals given under blood culture are number of colonies per c.c. of blood.

Case 42. D. P., a white boy, 11 years old, entered the hospital on the sixth day of illness which started with sudden, unaccountable pain in the left shoulder. On admission, he was acutely ill, cyanotic and feverish (103° F.). Physical examination revealed frequent extrasystoles, lobular pneumonia, and what was considered to be

osteomyelitis of the left shoulder. Blood cultures yielded hemolytic *Staphylococcus aureus,* and on subsequent osteotomy of the humerus, performed after the first injection of serum, the same organism was isolated. Both the bone and pulmonary infections were confirmed by roentgenographic study. The first injection of serum (60 c.c. intravenously) caused first a thermal rise and then a fall to normal. Because the skin test to carbohydrate was only partially positive, 40 c.c. of serum were given on the second day, and finally 20 c.c. on the third day. The chart demonstrates the rapid change brought about by the first introduction of serum.

In the large majority of patients recovering, however, the fall in temperature was more characteristically by lysis. Thus, the daily maximum and minimum temperatures dropped progressively so that a curve drawn halfway between each point for each day shows almost a straight line descending to normal and requiring from four to six days to reach that point.

The character of such a curve is represented in figure 2 and the history of the patient summarized.

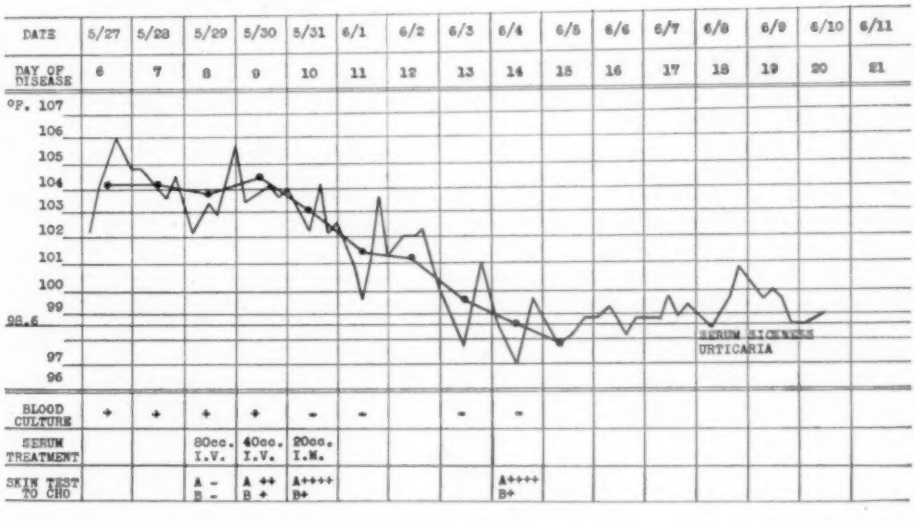

FIG. 2. Effect of Antiserum on Temperature. B. Fall by Lysis. Curve with black circles represents average daily temperature. Note progressive, daily fall.

Case 61. A white boy of 8 years entered the hospital on the sixth day of illness which followed an injury to the right knee. The clinical diagnosis of osteomyelitis of the femur was later verified by roentgen-ray films. The periosteum was incised immediately and a drain was inserted. On the eighth day of illness following two successive, positive blood cultures, 80 c.c. of serum were administered intravenously. The following day with the skin reaction to carbohydrate only partially positive, 40 c.c. more were given, also intravenously, and finally 20 c.c. intramuscularly on the third day. With two serum treatments, the blood culture became sterile, the skin reaction became strongly positive, and the temperature was on the downward trend, requiring six days before maintaining a normal range. Ten days following the first injection of serum there was a rise in temperature due to serum sickness, consisting of extensive urticaria which responded to symptomatic treatment within two days.

Occasional temperature graphs, on the other hand, may still show after serum therapy a more or less sustained fever. This type of reaction has been interpreted as suggesting the presence of foci of infection requiring drainage.

The following case offers a good example of this variety of fever (figure 3).

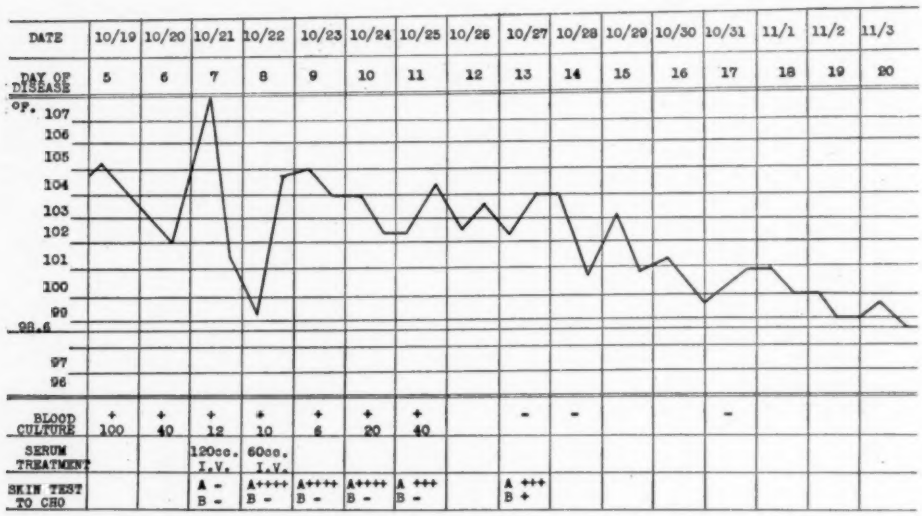

FIG. 3. Effect of Antiserum on Temperature. C. Interference by Foci Requiring Drainage.

Case 77. A white boy, 12 years old, was admitted on the third day of illness following a furuncle over the left scapular region, which had been squeezed two days previously. The chief clinical signs were obvious spread of infection to both lungs, in addition to septicemia. Serum was given on the seventh day, 120 c.c. intravenously, and on the eighth day, 60 c.c. Additional serum was considered unnecessary because of the strong reaction to Type A carbohydrate. It will be noticed (figure 3) that the temperature, nevertheless, remained high for five more days, and then gradually returned to normal. This is interpreted as signifying foci of infection (in both lungs) which required drainage, but because of their anatomical distribution were surgically inaccessible. Therefore, as long as natural drainage (i.e., absorption) went on, the temperature remained high.

Such examples add weight to the statement made above that when widespread metastases cause necrosis of tissues releasing toxic substances into the circulation, it is inevitable that the temperature should not be greatly affected by the serum.

Effect of Antiserum on Septicemia. It should be made clear that while bacteremia implies a transient passage of bacteria in the blood stream, septicemia implies either their constant presence or even their actual growth in the circulation, although not of the order of multiplication observed in vitro. In the case of staphylococcus the tendency to abscess formation with eventual extension beyond the abscess wall of the abscess contents leads to frequent bacteremia. Consequently, septicemia may be determined only by

frequently repeated blood cultures. It seems important to point out that the number of colonies per c.c. of blood does not carry the significance that a similar analysis does, say in pneumococcal infection. A study of hundreds of blood cultures made in this laboratory in connection with this investigation indicates clearly the enormous variation in colony counts and the frequent difficulty of reconciling them with the general clinical condition. Thus, in cases of endocarditis, the colony counts sometimes reach into the thousands, while in multiple lung abscess with massive destruction of pulmonary tissue the count may be very low or the blood may even be sterile, despite rapidly ensuing death. The frequent eruption of showers of organisms from local foci into the blood stream, and, conversely, the "filtration" of staphylococci

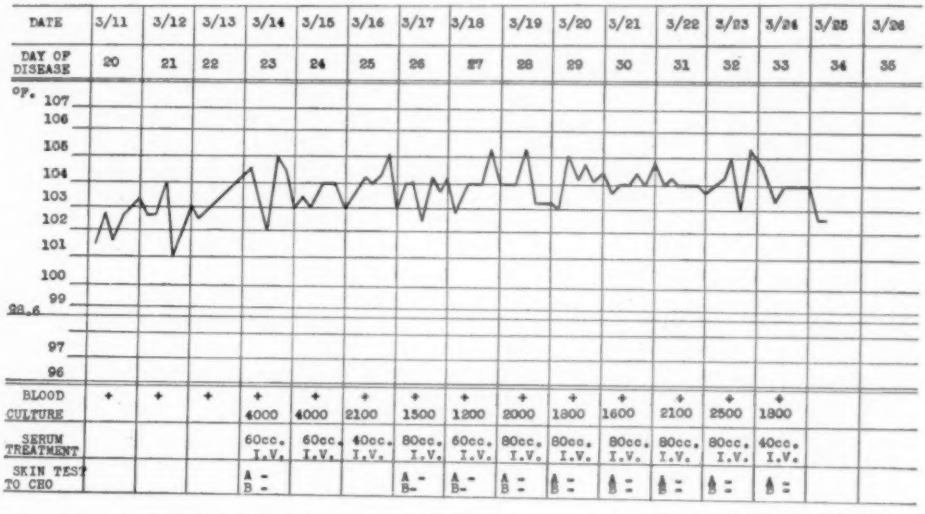

FIG. 4. Effect of Antiserum on Temperature. D. Inefficacy in Endocarditis.

by various organs and their artificial removal as capillary emboli in part due to their characteristic formation, may both cause marked variations in numbers which are difficult to reconcile with the general physical condition. Consequently, it is felt that information supplied by colony counts, unless these are uniformly progressive or approximately constant, may be misleading. In any case, it becomes pertinent to analyze the changes in septicemia accompanying the administration of antiserum.

As in the case of the temperatures described above, only a rare patient exhibited sterilization of the blood with a single injection of serum. The large majority of patients recovering required from two to four days or even more (figure 3), before attaining sterile blood cultures, and the colony counts made day by day were usually of the progressively decreasing variety. In order to illustrate sterilization of the blood in a particularly heavy septicemia, photographs of successive blood cultures are submitted in plate 2. This example was not selected as typical, since most septicemias do not reach

such a high point in colony count, but it is submitted as a demonstration of the potential clearing capacity of the serum, even though the case is unusual. Thus, it will be seen that a culture taken immediately before administering antiserum yielded *ca.* 400 colonies per c.c. of blood; on the next day preceding a second injection of serum, the count fell to 55 colonies; on the third

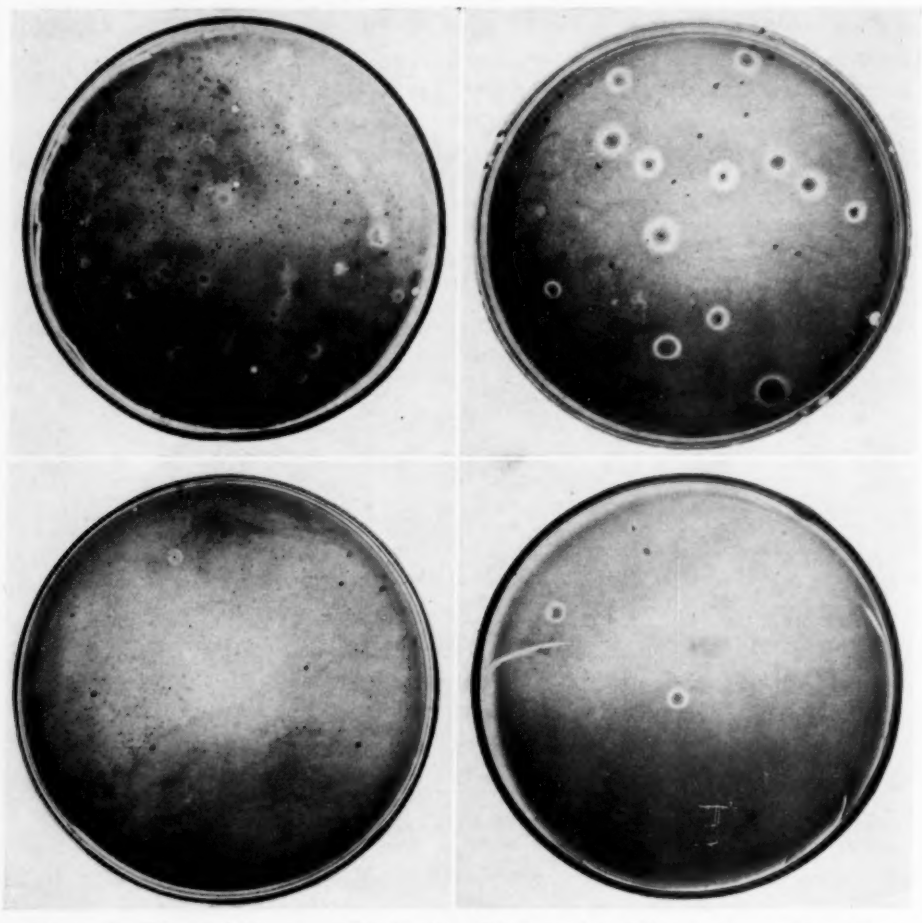

PLATE 2. Effect of Serum on Septicemia. Photographs of blood culture plates (1 c.c. of blood) made on successive days during serum treatment. Upper left, immediately before first administration, over 400 colonies; upper right immediately before second administration, 55 colonies; lower right, immediately before third administration, 20 colonies; lower left, immediately before fourth administration, nine colonies (*vid.* text).

day preceding more serum, the count fell further to 20 colonies; on the fourth day, before giving the last injection of serum, the count fell to nine colonies, and on the fifth day (after four injections of serum) the blood became sterile.

Effect of Antiserum on Skin Test to Specific Carbohydrates. Before starting serum therapy, skin reactions to the carbohydrates were not elicited

in any of the patients tested. While skin reactions to Type A polysaccharide may be demonstrated within an hour to an hour and a half following serum administration (which indicates how rapidly the antibody is distributed in the tissues), this was considered as transient and, therefore, unimportant from the aspect of recovery. Consequently, the skin reactions to be discussed are referable to those appearing 20 to 24 hours after giving serum. On this basis, it has been found that genuine reactions developed after two to four introductions of serum and occasionally the reaction obtained following the first treatment with serum was of sufficient intensity to indicate that further serum administration was unnecessary. When the reaction was once strongly positive the patients went on to recovery. It is interesting to add that thus far the skin reaction to Type A carbohydrate has not failed in its accepted interpretation (i.e., a measurement of immunity). As will be brought out later, the skin tests performed on the patients who died never elicited a skin reaction that could be regarded as definite. Occasionally, the reaction was actually classified as one plus, or even two plus, but this was obviously transient and due to the large quantities of recently administered serum.

Effect of Antiserum on Localized Lesions. In treating septicemia by intravenous or intramuscular application of antiserum a careful watch was kept on the different foci of infection. As a generalization it may be said that the antiserum exerted little activity on the original sites of infection, nor, as far as could be determined, on metastatic lesions. Several striking exceptions, however, were noted. Thus, in case 36, a white female, 23 years old, whose septicemia followed the pricking of a small abscess on the upper lip with an unsterilized sewing needle, there was massive swelling of the left face with edema of the lids, iritis, and metastatic pneumonia. Three separate abscesses developed in the iris, which the ophthalmologist in consultation considered sufficient grounds for enucleation. Simultaneously with serum therapy, given over five successive days, the abscesses receded with ultimately complete return to normal. In a second patient, case 13, a white male, 25 years old, whose septicemia followed the placing of gummed mending tape over a cut on the chin caused while shaving, the abscess caused tremendous swelling of the face and neck, and, subsequently, metastatic pneumonia. With serum treatment given on four consecutive days, the face and neck improved remarkably from day to day. The final example was a patient (case 50), a white female, 14 years old, whose septicemia followed by 24 hours a cut on the lower lip inflicted by a dentist's drill. She developed metastatic pneumonia and massive swelling and discoloration of the face and neck. Two administrations of serum were accompanied by sterilization of the blood, and definite, but not complete recession of the facial infection. In the pneumonic infections also serum therapy apparently caused a certain degree of improvement as evidenced by roentgenograms, but the changes were not as conspicuous as the preceding examples, and healing went on for

considerable time after serum had been discontinued. Consequently, the writer has not been greatly impressed with the effect of the serum on the localized lesions, and therefore, desires to emphasize again the great importance of utilizing surgical measures to create optimum conditions for accelerated and complete healing.

That the antiserum may have a preventive action on the formation of metastatic abscesses will be discussed later. Since the evidence for this opinion is best furnished by postmortem examination, it seems more appropriate to consider this point as part of the report on the fatal cases. At this point, however, attention may be drawn to the summary of case 83 (vide supra), which suggests the lack of metastatic infection accompanying the use of Type A antiserum.

Serum Reactions. This report would not be complete without a word of summary regarding the reactions induced by the antiserum. As stated early, the intravenous, trial dose given preliminarily to therapeutic administration was tolerated without difficulty by all the patients. In rare individuals, the first therapeutic injection had to be discontinued because of some troublesome reaction, as urticaria, respiratory difficulty, or decreasing pulse rate. This has already been alluded to above and need not be repeated here. In a certain number of patients, however, the symptom-complex recognized as serum sickness was also observed. Thus, in the 48 survivals, 17 (*ca.* 35 per cent) gave evidence of this complication. In each case there was a varying degree of urticaria, in some combined with edema, and in two patients, with arthritic pain and swelling. Serum sickness came on within nine to 14 days following the use of serum; it usually lasted 24 hours, occasionally 48 hours, and it always responded promptly to symptomatic treatment.

In this connection, an anomalous reaction worthy of note was encountered which has been difficult to classify. A boy of 15 years, with acute osteomyelitis of the left upper tibia was given 60 c.c. of serum intravenously on the day following osteotomy. After a thermal rise of 2 or more degrees to 105° F., the temperature began to fall, and within 16 hours after the injection, the temperature reached 95° F., where it remained for four hours. Finally, after various unsuccessful measures, an enema of hot, concentrated coffee was given, and, whether because or in spite of this treatment, the temperature began to rise, attaining normal within four hours, and 100.6° F. within 12 hours. From then on the patient recovered uneventfully with the temperature fluctuating only little above and below normal.

Recapitulation. The statistical analysis outlined above, then, discloses that if the data be accepted as they stand, Type A antiserum approaches a gradient of efficiency of about 50 per cent. Stated in other terms, it appears that the usual survival rate of 20 to 25 per cent has been doubled in the present study. Although less dramatic in its effect than antipneumococcal serum—unquestionably the most effective of the antibacterial sera in cur-

rent use—the indications are that in the ultimate analysis, Type A antistaphylococcal serum may provide comparable benefits, since both approximately double the usual survival rate of their respective infections. It must be remembered that the pneumococcus, although capable of causing massive infection, rarely destroys tissues or forms abscesses. The tremendous pulmonary involvement incited by this organism is characterized by a filling of the alveolar spaces with exudate which regresses so completely and benignly with recovery that no sign of the past infection remains. Surrounded by an ectoplasmic layer of carbohydrate, moreover, the organism reacts immediately with homologous antiserum, and it is, therefore, rapidly and effectively immobilized. In the case of the staphylococcus, on the other hand, the infection is essentially a process of abscess formation and tissue destruction with healing by cicatrization; and whatever the action between carbohydrate and antibody, it is necessarily delayed because of the endoplasmic distribution of the carbohydrate. It is small wonder, then, that antipneumococcal serum should initiate a more dramatic effect than antistaphylococcal serum.

The recoveries in this series represent different varieties of septicemic infection, as brought out in table 1. The primary focus varied from an infected pimple to the grosser diseases of pneumonia, meningitis or uterine infection resulting from self-induced abortion. The most impressive action of the serum, however, was witnessed in patients with osteomyelitis and septicemia. Thus, 27 such individuals were observed; of these 24 recovered, and three died. Of those recovering, only four have thus far returned for further care, as removal of sequestrum. Of those dying, one had reached the stage of endocarditis before administration of serum; one, pericarditis with a ruptured abscess of the heart muscle causing a direct communication between heart chamber and pericardial sac; and the third patient arrived at the hospital when the supply of serum did not permit adequate treatment. In this third case the blood was sterilized with the serum on hand, but the blood culture became positive again several days later. Because additional serum was not available, the patient received no more specific treatment, although in need of it. The condition became rapidly worse and within a week the patient died. Because of the complications in these three cases, it may be justifiable to attribute death to causes other than failure of serum.

In two other patients of this group, however, it was questionable whether the serum was of great assistance. In one the leg was finally amputated before recovery ensued, and in the other, despite the occurrence of a strong skin reaction to Type A carbohydrate, and precipitins in the blood to a titer of 1:200,000, the blood culture remained positive for several days before sterilization. Unless it is assumed that the antiserum prevented greater extension than was present, it must be admitted that the clinical condition changed very little, if any, during serum therapy. In any case, however, the ratio of survivals to deaths in this group is particularly high. It is felt

that gratifying results here were aided by the early administration of the serum in practically all the cases, and that, therefore, it is reasonable to deduce that if serum is to be given, then the sooner it is used, the greater its effectiveness.

Synopsis of Patients Dying

Upon analysis of those cases in which the infection proved fatal it soon became evident that death in many of the cases was inevitable since there was evidence that the infection had advanced beyond help by any form of treatment. During the past year, for example, the type of patients referred for serum treatment became particularly unfavorable due to prolonged, unsuccessful treatment with sulfonamides beforehand, as has already been brought out in a joint report from this laboratory and the Philadelphia General Hospital.[6] This resulted not only in the late administration of serum but frequently enough rendered prognosis hopeless. Consequently, if a fair estimate of the value of the serum is to be obtained, it is necessary to give a breakdown of the mortality figure. That a rapid impression may be gained of the factors entering into the death of the patients, certain data have been brought together in the form of protocols. In table 2, therefore, a summary of the fatal infections is given based on portal of entry. Of the 54 patients listed, seven became infected by way of furunculosis and miscellaneous

Table II

Summary of Fatal Infections Classified by Initial Infection

Total number of patients treated	102
Total number of patients dying	54
Furunculosis	7
Localized abscesses (miscellaneous)	7
Undetermined	7
Terminal septicemia (see text)	4
Pneumonia *	4
Osteomyelitis (see text)	3
Cellulitis	3
Sinus thrombosis (from infected pimple)	2
Sinus thrombosis (from panophthalmitis)	1
Drug poisoning with abscesses (see text)	2
Infection of foot	2
Draining chronic sinus	2
Postoperative infection (prostatectomy)	1
Otitis media (bilateral)	1
Endometritis (spontaneous abortion)	1
Perinephric abscess	1
Infected scratches (see text)	1
Pemphigus with cellulitis	1
Pneumonia following chickenpox	1
Leukemia with unexplained septicemia	1
Nephrosis with multiple abscesses	1
Infected pimple with pneumonia and endocarditis	1
Total	54

* In addition to the primary pneumonias listed, there were 12 examples of metastatic pulmonary infection.

localized abscesses; while in seven others the original focus was not satisfactorily established. Staphylococcal septicemia terminal to some other preexisting condition (congenital jaundice, twice; malnutrition and congenital heart disease once each) was encountered four times, and in four others the primary lesion was in the form of pneumonia. In the latter connection, it should be pointed out that in addition to the primary pneumonias, there were 12 examples of metastatic pneumonia. Three more cases started by way of osteomyelitis as already discussed above. The remaining 22 patients represent a miscellaneous group, for the most part, of individual examples, as tabulated.

If, now, the fatal infections are reclassified on the basis of various factors entering into and, perhaps, contributing to the serum failures, a number of interesting features are brought to light. This information is summarized in table 3, and lends itself most readily for presentation under the topical order employed therein.

TABLE III

Summary of Miscellaneous Factors Contributing to Serum Failures

Factor Encountered	Number of Patients	% of Total Treated
Patients with endocarditis	15	15
Patients dying within 72 hours	15	15
Death due to other causes	5	5
Serum treatment excessively delayed	4	4
Patients with pericarditis	3	3
Patients with sinus thrombosis	3	3
Miscellaneous	9	9
Total	54	54

Patients with Endocarditis. Of the 54 patients dying during serum treatment, 15 (or 15 per cent of the total treated) gave clinical evidence, before serum was started, of endocarditis which was subsequently confirmed at postmortem examination. This condition proved to be invariably fatal. The bacterial count of the circulating blood always ran high (hundreds or thousands of colonies per c.c.) and did not appear to be influenced by the serum. In order to illustrate the ineffectiveness of Type A antiserum in endocarditis a brief résumé will be given of case 51.

Case 51. A white girl of 13 years entered the hospital after two weeks of high temperature, severe "cold" with general malaise, occasional chills and frequent urination (two and three times an hour). She was treated with sulfapyridine until the twenty-third day when serum was administered, at a time when endocarditis had become clinically evident. The patient received a total of 640 c.c. of serum intravenously over 11 days without affecting the general condition, the skin test to carbohydrate, or the septicemia which ran from 1200 to 4000 colonies per c.c. of blood. At postmortem examination there was found a massive vegetation of the tricuspid valve, almost completely obliterating the lumen.

It is the writer's opinion that in staphylococcal endocarditis the prognosis is unfailingly fatal and no method of treatment now exists for alleviating or arresting this condition. It is felt, however, that since *so often* endocarditis is a later development of septicemia, early, adequate treatment may prevent its occurrence in at least a certain proportion of the patients.

Patients Dying Within 72 Hours. That a large share of the patients studied were referred when the prognosis was poor is evidenced by the 15 individuals (15 per cent of the total number) who died within 72 hours after starting serum. In fact, two-thirds of this number died within 48 hours. It is readily seen how hopeless the condition was, and in any case, this group cannot be considered as a fair trial for any experimental treatment.

Death Due to Other Causes. Five patients of those dying are, curiously enough, examples of successful treatment despite fatal termination. In each individual the septicemia had been eliminated, and the patient was apparently improving when death intervened through a superimposed condition. Thus, in an elderly man, the complication was lobar pneumonia due to pneumococcus, Type VIII; in a child, hemorrhage of the carotid during an operation of the throat caused exsanguination; in a middle-aged man under treatment for syphilis, in whom there was originally arsphenamine poisoning with dermatitis which became the primary site of infection, death was due to arsenic poisoning as autopsy later demonstrated; in the fourth (case 83 above) subsequent invasion of the blood stream by hemolytic streptococci was the final cause of death; in the fifth patient, the original difficulty was a perinephric abscess which was treated surgically by nephrectomy with subsequent infection at the site of operation; the septicemia and local infection subsided but there was a persistent pulmonary infection which after about three months caused death. Up until autopsy, the lung involvement was considered staphylococcal in nature, but this was an erroneous assumption since the process revealed itself as one of actinomycosis, probably even antedating the staphylococcal infection. It is important that staphylococci were not recovered from heart blood cultured at postmortem examination and that the organs and tissues were free of metastatic abscesses.

Serum Treatment Excessively Delayed. Further analysis discloses that four patients were started on serum late in the disease. After this study was under way, it was anticipated that a certain proportion of the patients would be treated at a later date than desired. In these four, however, the delay exceeded any anticipations. Thus, serum treatment was started on the twenty-eighth, fifty-first, fifty-second, and fifty-eighth days of illness, respectively. Perhaps the surprise should be not that the serum failed to check the infections, but that the patients lived as long as they did.

Patients with Pericarditis. Three other patients had extensive pericarditis when first seen. In two (including the one mentioned above) an abscess in the myocardium had ruptured into the pericardial sac. In both cases leaking blood had clotted and become adherent to the visceral and parietal peri-

cardium. Numerous small colonies of staphylococcus were distributed throughout the clot. As with the cases of endocarditis these must be considered as failures on the part of the serum, and, most probably, hopeless complications of staphylococcal infection.

Patients with Sinus Thrombosis. There were three instances of this condition, each further aggravated by secondary meningitis. All three patients died, leaving no doubt that the serum had been of no benefit. It seems that as in the case of cardiac infection, sinus thrombosis is beyond help by this serum.

Miscellaneous Patients Dying. In three other individuals death was unquestionably due to staphylococcal infection, but in each instance a type of complication had arisen which placed the predominant focus beyond the reach of serum. Thus, in an elderly diabetic (case 20), there had been a thrombophlebitis of the femoral vein extending from the knee to an inch beyond the bifurcation of the vena cava. The circulation had been completely blocked and a huge clot riddled with innumerable colonies of staphylococci extended along the distance described. The second example was an elderly man (case 35) who fell from a ladder, scraping his thigh which was the original focus of infection, and suffering retroperitoneal hemorrhage presumably from the left kidney which was not suspected until autopsy. Apparently the bleeding continued at a reduced rate for some time following the accident, and at autopsy there was a massive blood clot adherent to the left kidney and studded with staphylococcal colonies. The third case was a diabetic of long duration (case 81) whose infection started by way of a boil in the sacral region and eventually reached the prostate gland. At postmortem examination there was revealed for the first time more or less complete destruction of the prostate with a large pocket of pus in its place that had eroded through the rectum causing open passage (fistula) between this area and the intestinal canal. It is interesting that in the first two patients no metastatic abscesses were located at autopsy; while in the last the only abscesses found were several scattered ones in both kidneys, a surprisingly slight degree of dissemination considering the nature of the case, the infection, and duration of septicemia (*ca.* two weeks).

In one of two patients with pneumonia (cases 48 and 49) the disease was secondary to influenza, and in the other to a boil on the left shoulder following "home treatment." In both instances the infection at first treated with sulfonamides did not respond to serum given daily over six and eight days respectively.

The last four patients represent miscellaneous conditions. In one (case 34) a young infant with congenital icterus, the septicemia was considered terminal. It did not respond to serum treatment. Case 41 was already suffering with paresis including a dissecting aneurysm of the aorta, and tuberculosis of the spine. The latter caused almost complete destruction of the third lumbar vertebra at which site staphylococci first appeared. He was treated intensively with antistaphylococcal serum without clearing of the

original focus, receiving 280 c.c. of serum over a period of four days, with sterilization of the blood. He nevertheless died one week following the last injection of serum. Death in the third patient, a young male adult (case 19) was described by the physician in charge as due to a "gross diagnostic error." A diagnosis of meningitis and septicemia had been made, and serum was given intravenously and intrathecally; the blood culture became sterile, meningeal symptoms disappeared and the patient was apparently improving when death came unexpectedly. At autopsy a large paravertebral abscess was found. It was so close to the surface that drainage would have been a simple matter with possibly a different outcome. Postmortem examination disclosed no metastatic abscesses in the organs and tissues. The final patient is the one referred to previously who entered the hospital with osteomyelitis and septicemia at a time when the supply of serum was particularly low.

Analysis of Postmortem Observations. Of the 54 patients dying, autopsies were performed on 37, it being impossible to obtain the necessary permission in the remaining 17. Study of the 37 bodies revealed that extensive metastatic abscesses were demonstrable in 21, while in two the number of metastatic abscesses appeared to be less than had been anticipated. In 11 of the remaining 14 no metastases were found; in three, however, there were hemorrhagic infarcts in different organs. The indications are, therefore, that with due consideration of the early deaths, the patients with endocarditis, and the delayed serum treatment in the instances cited, the proportion of cases appears high in which visceral dissemination was not observed. In any case, the rate as it stands is about 30 per cent.

In rapid fulminating infection terminating fatally, it is possible that no metastatic abscesses may occur, since abscess formation requires a certain interval of time. Since the cases reported here were for the most part prolonged infections, it seems not unlikely that prompt administration of serum may reduce the spread of infection to the different organs and tissues.

Recapitulation

That the data derived from this study might be examined at a glance, the final results of serum treatment have been appended in table 4 in the form of a classification by chief clinical symptoms. As stated above, osteomyelitis was the most frequent forerunner of septicemia and responded best to serum with a survival of 24 out of 27 patients. Endocarditis occurred next in frequency in 15 patients. This condition was completely refractory to Type A serum and was characterized by uniform fatality. Of 14 patients with furunculosis and varying metastatic infection, seven survived and seven died. Primary pneumonia contributed eight patients with four deaths and four survivals. In this connection may be mentioned 22 patients with pneumonia secondary to a primary surface lesion; 12 died and 10 survived. Four patients each with cellulitis with metastases, and septicemia terminal to

some other condition, were treated with antiserum and all died. Pericarditis and sinus thrombosis with secondary meningitis occurred in three patients each, and was fatal in every instance. Primary meningitis seen three times, and endometritis following abortion seen twice ended with recovery in each case. The remainder forms a group of 19 patients with a variety of conditions representing for the most part individual examples. The end result in this group showed eight recoveries and 11 deaths. It may be of interest to add that staphylococcal septicemia was encountered in diabetes on five occasions. Although they all died, it is felt that there were other factors involved, so that the combination of diseases need not necessarily imply a fatal termination.

TABLE IV

Final Results of Serum Treatment, Classified by Predominant Clinical Symptoms

Chief Clinical Manifestation	Number of Patients				% Recovery
	Treated	With Septicemia	Survived	Died	
Osteomyelitis	27	26	24	3	89
Endocarditis	15	15	0	15	0
Furunculosis with metastases	14	14	7	7	50
Pneumonia	8	5	4	4	50
Cellulitis with metastases	4	4	0	4	0
Terminal septicemia	4	4	0	4	0
Pericarditis	3	3	0	3	0
Sinus thrombosis	3	3	0	3	0
Endometritis following abortion	2	2	2	0	100
Meningitis	3	3	3	0	100
Miscellaneous	19	19	8	11	45
Total	102	98	48	54	47 (average)

That the therapeutic results are perhaps dependent upon the activity of the serum rather than some personal factor of management may be seen in a comparison of the statistics collected in different areas. Examination of the data assembled in table 5 illustrates the results obtained from St. Louis and vicinity by the writer, from the Philadelphia General Hospital, and from scattered cities throughout the country to which serum has been sent on request. Thus, in St. Louis, 62 patients were treated with a recovery rate of 45 per cent; in Philadelphia, there were 22 patients with the same rate; and the scattered cases represent 18 individuals and a therapeutic efficiency of 55 per cent. The 10 per cent difference among the three was probably influenced by the fact that all but two cases of endocarditis and all of the cases of sinus thrombosis and pericarditis occurred in the St. Louis and Philadelphia groups.

If the running summary supplied above on the fatal infections actually depicts what have been considered as unusual conditions of study, it is possible that Type A antiserum has greater therapeutic value than has been demonstrated. The large number, alone, of hopeless patients accepted for

treatment (15 dying early, four treated excessively late, together with the 18 presenting cardiac infection) accounts for better than two-thirds of all the deaths. However, until statistical evidence of sufficient magnitude becomes available from different sources, the therapeutic potentiality and appraisal of Type A antiserum must remain in abeyance. In the meantime, no amount of explanation and theorization can affect the final outcome.

TABLE V

Comparison of Therapeutic Effectiveness of Type A Antiserum in Different Areas

Locality	Number of Patients			% Recovery
	Treated	Survived	Died	
St. Louis	62	28	34	45
Philadelphia	22	10	12	45
Scattered	18	10	8	55 *
Total	102	48	54	47

* Oddly enough, only two cases of cardiac involvement are included in this group which may help to explain the higher percentage.

DISCUSSION

Since pathogenic staphylococci are phagocytized by so-called normal cells, it is necessary in any discussion concerning treatment to include the possibility of nonspecific activity. Obviously, if a therapeutic agent stimulates leukocytosis, for example, then the degree of phagocytosis taking place may well be proportionately enhanced. With increase in phagocytosis, one may logically assume synchronous promotion of bacterial immobilization and finally disintegration. To this extent, then, any treatment incorporating foreign proteins, toxic split products, etc., might conceivably be of benefit, and in certain instances of not so severe infection, it might afford the assistance required for recovery. In more or less critical disease bacterial elimination imposes greater demands on the treatment which may explain the limited success of some of the agents introduced in the past (e.g., foreign proteins, toxic metals, antivirus of Besredka, bacteriophage, and even antitoxin in which, however, there is a degree of specificity as well). That Type A antiserum possesses a distinct specific element is indicated by the observations in case 83 described above, and by certain experiments still under study on the antibody analysis of this serum. It seems to the writer that although Type A antiserum undoubtedly possesses nonspecific properties, its additional value resides in its specific (i.e., anticarbohydrate) constituent.

The data already reviewed suggest that Type A antiserum may have a certain value in the treatment of staphylococcal septicemia accompanying a variety of clinical manifestations. While the current rate of survival has been close to 50 per cent, it is felt that with better application of the principles of serum therapy and better understanding of the nature of staphylococcal

infection, this proportion may possibly be raised in the future. Thus, if serum is administered as soon as indicated, if surgical drainage is instituted as soon as feasible, and if the supportive care suggested at the time is supplied, then the antiserum would be given optimum conditions for testing its therapeutic capacity. It must be remembered that prolonged staphylococcal septicemia invariably leads to widespread abscess formation, and as the abscesses become numerous, the prognosis becomes grave; first, because the abscesses intensify the septicemia by discharging into the circulation, and second, because the abscesses are more frequently than not surgically inaccessible. The logical treatment, therefore, should be directed toward elimination of septicemia and prevention of metastatic infection. That Type A serum may actually accomplish this end, in certain cases, at least, is exemplified by the patients who survived and those who reached the autopsy table without metastatic foci despite extended septicemia.

It is desirable to emphasize again the importance of surgical drainage. Evidence reviewed above indicates the inability of the antiserum to control localized lesions. It is necessary, therefore, to evacuate abscesses by artificial methods. This aids not only the elimination of innumerable staphylococci but allows the escape of the toxic substances formed by the bacteria and by tissue destruction.

Summary and Conclusions

1. Ninety-eight patients with staphylococcal septicemia and four with severe infection without septicemia have been treated with specific Type A antibacterial serum prepared in rabbits.

2. All the staphylococci isolated in this study fermented mannite and contained Type A carbohydrate. None of the strains was particularly virulent for white mice. About half of the strains were tested in rabbits, and a lesser number in guinea pigs; their virulence for these animals also was considered low.

3. In addition to the antiserum, treatment included surgical drainage and supportive care.

4. Of the patients treated, 48 survived and 54 died; in the latter group there were five patients who, although dying of other causes, recovered from the staphylococcal septicemia.

5. Type A antiserum exerted its greatest effect in osteomyelitis present with septicemia; 26 patients were treated, and 23 recovered; three died as explained above. An additional patient with bacteremia recovered.

6. The least promising results were observed in cardiac infection and sinus thrombosis; there were 18 patients in the former group and three in the latter, all of whom died.

7. Of the 54 patients dying, 15 succumbed within 72 hours after starting serum; this and other conditions tabulated in the text suggest that all the

failures may not have been entirely due to impotency on the part of the antiserum.

8. The data indicate at this time a twofold increase in the usual survival rate, but actual evaluation of the serum will have to await future work from different sources.

Addendum

Since this article went to press, six additional patients have been treated with Type A serum according to the procedure described in this paper. Four of these patients survived and two died. Those recovering were all examples of septicemia secondary to (1) apparently sinus thrombosis, (2) osteomyelitis, (3) pneumonia, and (4) furunculosis. Those dying were patients with septicemia and (1) endocarditis, (2) brain abscesses.

Note. It is not practical at this time to thank the numerous physicians, surgeons, and nurses who have contributed so graciously to this study. Special acknowledgment, however, must be made to Drs. Alexis F. Hartmann and David P. Barr of St. Louis, Drs. Harry G. McNamee and the late Robert G. Torrey of Philadelphia, and the Lederle Laboratories and the Eli Lilly Co.

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WILLIAM WITHERING: HIS CONTRIBUTION TO MEDICINE*

By JONATHAN C. MEAKINS, F.A.C.P., *Montreal, Quebec, Canada*

ON March 17 of the year 1741, two hundred years ago, there was born at Wellington, in Shropshire, to Edmund Withering and his wife, Sarah Hector, a son who was to be known as William. The event was not heralded by any celestial phenomena or terrestrial disturbances.

Our scene really opens in the latter half of the century, a period of intellectual, scientific and political unrest and consequent progress. The seeds of independence and freedom of man were in the state of germination. The writings of Rousseau and Hume were influencing men's political outlook. The American revolution against traditional privilege or so-called tyranny was in the offing in spite of the Pitts, father and son, and of Charles James Fox; the cloud as small as a man's hand foretelling the bloody French revolution was barely visible on the political horizon; and Frederick the Great was seeking to weld a new Teutonic order in Europe.

In more peaceful mold Watt was developing the steam engine; Murdock invented gas-lighting; and Davey was soon to perfect his lamp. Black and Priestley were making notable advances in chemistry; the Munroes, Cullen and Hunter, were outstanding figures in Medicine; and Adam Smith was laying the basis for our present science of economics.

It was in this environment of teachers and companions that William Withering entered his professional life and training in Stafford and later Birmingham. The therapeutic era of bleeding, emesis, purgation and clysters was drawing to a close—although it knew it not—to be replaced by the little less tragic period of polypharmacy.

The record of William Withering's career at Edinburgh does not reveal any outstanding feats of academic excellence. He apparently took advantage of all the University could give in the way of education, social contacts and student activities. He undoubtedly spent his time and money to good purpose and returned to practice his profession in the small town of Stafford not far from his birthplace, in the Marches of Wales. The choice of this place as against the region where his family had been well known as physicians for generations reveals an independence of action which up to this time would not have been expected. He seems to have been possessed of all the virtues and few if any of the vices of the young men of his day. Wine, women and song do not appear to have entered into his life, even when on the traditional "grand tour" of the Continent, if one is to believe the whole tale as told in letters and the character of his companions. I may do him an injustice, but I am afraid not!

* Read at the Boston meeting of the American College of Physicians April 22, 1941.

Apparently it was in 1767, his twenty-seventh year, that Withering began to practice. I cannot help but believe that he was one of those whose intellectual growth comes relatively late and is forced into bloom by extraneous influences comparable today to the use of ultraviolet light in henneries or a shot of vitamin B complex to plants and flowers. He had, up to this time, been interested in geology, mineralogy and antiquarian matters which were all of a highly respectable character. The science of botany had experienced a slight rejuvenation during the Renaissance but, in a medical sense, had remained in the hands of the apothecaries, herbalists, " old women," and many others whom we would today class as " irregular practitioners " in our most disdainful manner. It is true that the publication of " Flora Lappoinca " by Linnaeus (1737) gave an indication of the future, and later in the same year the appearance of his " Genera Plantarum " and in 1738 his " Classes Plantarum " initiated modern systematic botany. Natural history was experiencing a fashionable boom at this time, so it was but natural that Withering should join in the tide, as he did in the other social activities of the time, such as lawn bowling, amateur dramatics, and musicales; he even played the flute and Scottish bagpipes—a hang-over from his student days in Edinburgh. It would seem that a more primitive urge than either science or society led him to the pursuit of botany.

One of his first patients was Miss Helena Cooke to whom he would appear to have had a softer attachment than that engendered by a lucrative patient. Miss Cooke was also a young lady of the period, as she indulged in flower painting. It is not clear whether this was after the manner of occupational therapy or a really social urge. However that may be, Withering on the meagre rounds of his practice, or perhaps during lovesick strollings through the meadows, collected and brought to her flowers and plants as models for her artistic endeavors. So began his interest in botany which eventually culminated in his publication in 1776 of " A Botanical Arrangement of All the Vegetables Growing in Great Britain with Descriptions of the Genera and Species According to Linnaeus." A most portentous title as is proper for such a subject! There was little that was original about this volume unless it were that it was written in English and was apparently considered to be a complete account of these bucolic plants; actually much of it was really a translation from the Latin of other texts. There were included 12 copper plates which apparently were not after the paintings by his wife; if they had been, it would have been a delicate touch of collaboration. Although this book was a best seller, Withering's original work lay more in chemistry and geology. He was specially interested in the composition of the water of the medicinal springs and spas of Great Britain, and in mineralogy was the discoverer of native barium chloride which was later named " Witherite " in his honor.

It would seem apparent that his interest in medicinal waters was the first indication that his thoughts were being directed to therapeutics. In the

medical writings of the period dropsy was as baffling a problem as its synonym "edema" is today. It was, therefore, quite logical that the gossip of a supposed cure by some herbal concoction should have intrigued a botanist and a therapeutist. It is a well known tale of how Withering was asked his opinion of a family (and supposedly secret) remedy for dropsy, known to an old woman of Shropshire, his home county. This concoction contained some 20 or more ingredients. Of these Withering states "It was not very difficult for one conversant in these subjects to perceive that the active herb could be no other than foxglove." This statement would strongly suggest that the foxglove had a local reputation at least in domestic medicine even if it had not reached the dignity of being included in the official pharmacopoeia of the time. It is not really surprising that this should have been so. In fact, Withering did not discover digitalis as much as the foxglove discovered Withering. It was a common weed of the countryside with a virtuous reputation of good works in Shropshire, Warwickshire and Yorkshire, and probably elsewhere, which needed a discrete press agent rather than a discoverer. That Withering fulfilled this part is much to his credit. One has only to read the account of some of his cases of which the following is a good example, to appreciate what a boon this drug was then as it is today.

CASE XCIV

"July 5th. Mr. C....., of W....., Aet. 28. Had drank very freely both of ale and spirits; and in consequence had an ascites, very large legs, and great fulness about the stomach. He was ordered to take the Infusion of Digitalis night and morning for a few days, and then to keep his bowels open with chrystals of tartar. The first half pint of infusion relieved him greatly; *after* an interval of a *fortnight* it was repeated, and he got well without any other medicine, only continuing the chrystals of tartar occasionally. I forgot to mention that this gentleman, before I saw him, had been for two months under the care of a very celebrated physician, by whose direction he had taken mercurials, bitters, squills, alkaline salts, and other things, but without much advantage."

It should here be stressed that popular belief attributed the virtue of digitalis to the vomiting and purgation which it induced. Withering knew better than this and rightly sought to induce diuresis without the toxic symptoms almost constantly induced by massive doses, as recounted in the following case.

CASE CVI

"November 2d. Mr. S....., of B.....h....., Aet. 61. Hydrothorax and swelled legs. Squills were given for a week in very full doses, and other modes of relief attempted; but his breathing became so bad, his countenance so livid, his pulse so feeble, and his extremities so cold, that I was apprehensive upon my second visit that he had not twenty-four hours to live. In this situation I gave him the Infusion of Digitalis stronger than usual, viz. two drams to eight ounces. Finding himself relieved by this, he continued to take it, contrary to the directions given, after the diuretic effects had appeared.

"The sickness which followed was truly alarming; it continued at intervals for many days, his pulse sunk down to forty in a minute, every object appeared green to his eyes, and between the exertions of reaching he lay in a state approaching to syncope. The strongest cordials, volatiles, and repeated blisters barely supported him. At length, however, he did begin to emerge out of the extreme danger into which his folly had plunged him; and by generous living and tonics, in about two months he came to enjoy a perfect state of health."

Withering knew well the symptoms and signs of digitalis intoxication. It was his constant endeavor to combat the folly of the laity and the profession in the use of the drug. Furthermore, he acknowledged his ignorance of the proper dosage and was constantly striving to devise a safe method of standardization which was not accomplished until a century and a quarter had passed. He appreciated that the drug varied in concentration in different plants, in different parts of the same plant, and at different times of the season, and finally he determined that different manners of preparation were of greatly varied potency. He eventually advised that the leaves should be gathered just before blossoming time, the midrib removed, and the leaf blade alone dried in the sun or before a fire. They were then ground to a fine powder and the dose for an adult was one to three grains of this powder twice a day. How modern this sounds!

Many have praised William Withering for the introduction of foxglove into our therapeutic armamentarium. This does not impress me nearly as much as the fact that he *kept* it there. He knew full well that the vomiting, diarrhea, bradycardia, cardiac arrhythmias, visual disturbances, sudden death, etc., were due to excessive amounts of the drug.

Case CVII

"November 19th. Master S....., Aet. 8. Ascites and anasarca. A dram of Fol. Digitalis in a six ounce infusion, given in doses of a spoonful, effected a perfect cure, without producing nausea."

He continued to emphasize that diuresis was the optimum objective. Even though he attributed this to a direct action on the kidneys and did not consider its cardiac effect, this in no way detracts from his contribution to Medicine. He was conscious, however, that it had an influence on cardiac function since in the ninth and last of his inferences he states "that it has a power over the motion of the heart, to a degree yet unobserved in any other medicine, and that this power may be converted to salutary ends." This statement was probably based upon shrewd observations of the pulse, as revealed by the following excerpts from his records:

Case II—before treatment "her pulse was extremely weak and irregular": after digitalis "her pulse became more full and regular."

Case XX—"sudden violent palpitation of his heart"—infusion as before which very soon removed his complaints.

Case XXXI—"her pulse very small and slow": digitalis had been given by a colleague who had seen Withering prescribe it before, but he had not "attended to

stop the exhibition of the medicine when its effects began to take place. The great distress of her situation was evidently owing to the imprudent and unlimited use of Digitalis. The third day the pulse was not so slow."

Case LXXVIII—" it lowered his pulse."

Case CVI—already mentioned.

Case CXVII—" at length I was urged to give the Digitalis, and considering the case as desperate, I agreed to do it. The event was as I expected; no increase in the urine took place; and the medicine being continued, his pulse became slow, and he apparently sunk under its sedative effect. He was neither purged nor vomited; and had the Digitalis been omitted altogether or suspended upon its first effects upon the pulse being observed, he might perhaps have existed a week longer."

Case CXXI—" Pulse 132 . . . I mention this case . . . to point out the great effect the Digitalis has upon the heart; for the pulse came down to 96.. and the pulse never became quicker."

Case CXXIX—" The intermitting pulse . . . he recovered his usual health."

Case XXXII—" pulse 160 tremulous beats in a minute, but the pulsation in the carotid arteries was such as to be visible to the eye, and to shake his head so that he could not hold it still." The diagnosis seems in little doubt but there is no further mention of the pulse.

Case CLXII—" his pulse very small and quick "—no further mention.

Mr. Causer's 1st case—" an irregular pulse "—no further mention.

Mr. Causer's 2nd case—" a very irregular, intermittent pulse." " Pulse better."

Dr. Stokes' 1st case—" Pulse irregular, with frequent intermissions "—no further mention.

Dr. Stokes' 3rd case—" Pulse intermitting "—no further mention.

Mr. Young's 1st case—" the pulse small and quicker than usual "—no further mention.

Mr. Young's 2nd case—" the pulse varying between 94 and 100 and feeble—no further mention.

Mr. Young's 3rd case—" his pulse feeble and intermitting " after it is stated " The pulse in a few hours became regular, slower and stronger."

Mr. Young's 5th case—" The pulse exceedingly strong and rebounding beating 114 to 120 every minute "—Corrigan—neither digitalis nor " Repeated bleeding had any effect in diminishing the violent action of the heart."

Mr. Young's 8th case—" Pulse feeble "—no further mention.

From some 212 cases of his own and those reported to him by his colleagues the pulse is mentioned only 19 times, but it is only in nine cases, seven of which were reported by Withering and one by Young, that any after effect upon the pulse is noted, and in seven it is stated that it became slower. This is not much evidence upon which to base his ninth inference, but it was more than anyone else had noted at the time and not much less than was known a hundred years later when Mackenzie published his epochal work.

Withering used the drug for many conditions which would seem to have included congestive failure, nephritis, cirrhosis of the liver, tuberculous peritonitis, pulmonary tuberculosis, ovarian cyst, etc. There is no doubt that he had a shrewd idea that it was much more efficacious in some of these than in others, but at no time does he definitely commit himself. This may have been due to his native modesty, although I should doubt it. He was not given " to hiding his light under a bushel," but rather to an appreciation of his superior knowledge—which is always an asset in this life.

It was in 1775 that he started to use this drug. In 1783 digitalis was included in the Edinburgh Pharmacopoeia, which was two years before the publication of his "Account of the Foxglove." This book was not published to introduce digitalis but to preserve it, as Withering definitely states in the following words:

> The use of the Foxglove is getting abroad and it is better the world should derive some information, however imperfect, from my experience, than that the lives of men should be hazarded by its unguarded exhibition, or that a medicine of so much efficacy should be condemned and rejected as dangerous and unmanageable.

His published notes on cases constantly reiterate caution and point out the drug's dangers and virtues in a manner that could not be surpassed by any other means. As he said "Poisons in small doses are the best medicines, and the best medicines in too large doses are poisonous." But have we taken advantage of this great contribution to our therapeutics? I hazard to answer this question in the negative. I am sure William Withering would turn in his grave if he knew that today, 142 years after his death, digitalis poisoning is the most common intoxication encountered in the medical wards of a general hospital.

If William Withering were given to profanity, which I greatly doubt, I can hear him cry: "God's blood! How can they be so damned foolish after all my admonitions!"

CASE REPORTS

ACUTE HEMOLYTIC ANEMIA CAUSED BY SULFATHIAZOLE*

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The first case of hemolytic anemia resulting from sulfanilamide was reported by Harvey and Janeway [1] two and a half years after Domagk had introduced this drug into clinical medicine in 1935. Since then a number of similar reports have appeared, and W. B. Wood [2] found the incidence of this toxic reaction to be as high as 4.0 per cent in his series of 522 cases at the Johns Hopkins Hospital. Two fatal cases [3, 4] have already been described. The sulfapyridine derivative, introduced by Whitby in 1938 primarily as an effective chemotherapeutic agent against the pneumococcus, offered, in addition, the not unimportant advantage of provoking less serious toxic reactions insofar as the hemopoietic system was concerned. The number of reported cases of hemolytic anemia resulting from sulfapyridine has been very few, though recently Ravid and Chesner [5] have reported the first fatal case. Sulfathiazole, first described by Fosbinder and Walter [6] and by Lott and Bergeim [7] in 1939, has been found to be as effective as sulfapyridine in the treatment of pneumococcus pneumonia in man and possibly more effective in staphylococcus infections.[8] Spink and Hansen [9] report that "there is no doubt that sulfathiazole is more effective than sulfapyridine in the treatment of staphylococcic septicemia and appears to be the best therapeutic agent available for this infection at the present time." The low toxicity of this substance in the experimental animal and in man has been emphasized by several workers.[10, 11, 12] In the series of 100 patients treated with sulfathiazole by Flippin, Schwartz and Rose [12] and among the 128 patients treated by Spink and Hansen,[9] hemolytic anemia did not occur once. Because of its therapeutic superiority over sulfapyridine in certain infections and because of its comparatively low toxicity, sulfathiazole is used as widely as sulfanilamide or sulfapyridine. The various toxic reactions that may result from this drug should, therefore, be known. It is primarily for this reason that we wish to report a case of severe hemolytic anemia resulting from sulfathiazole.

Case Report

A white male of 38 was admitted to Beth Israel Hospital, N. Y., on September 11, 1940 in the private service of one of us. He had been ill since September 3 and under the care of a local physician until he was admitted to the hospital. His illness began with a cellulitis of the dorsum of the left foot resulting from a secondarily infected toe originally the site of dermatophytosis. Four grams of sulfathiazole were given on the first day, 3.0 grams on the second, 2.0 grams on the third and 1.0 gram each day for the next three days. This chemotherapy was supplemented by ultra-violet radiation to the foot from the second to the seventh day of illness. A 110 volt mercury arc

* Received for publication October 25, 1940.

lamp was used at a distance of 8 inches, at first for 10 minutes and then for 25 minutes three times a day. During the first few days of sulfathiazole medication the patient's temperature returned to normal but he complained of an "acute binding sensation" in the lower abdomen which had a girdle-like distribution and was vise-like in character. On the sixth day of illness the cellulitis spread from the dorsum of the foot to the lower two-thirds of the leg and the temperature rose abruptly to 105.5° F. The patient had a severe shaking chill and again became acutely ill.

At this point the question of sulfathiazole toxicity was carefully considered. A blood count showed 4,300,000 red blood cells, 86 per cent hemoglobin, 7,500 white blood cells of which 72 per cent were segmented polymorphonuclears, 10 per cent non-segmented neutrophiles and 18 per cent lymphocytes. The urine showed no abnormal changes. Because the cellulitis had spread and was associated with a rise in fever, because the blood picture showed no unusual changes and the patient was not jaundiced, and finally, because only 12 grams of sulfathiazole were given in six days, it was decided to increase the dosage to a little more than five grams the next day. This was administered on the seventh day. Twenty-four hours later the patient became much worse, though his cellulitis was subsiding. He now complained of a dull, unlocalized pain "fleeting from head to foot like a ghost" but centering mainly in the abdomen. He also, on questioning, said he had some tinnitus and impaired hearing. He vomited three times, had complete anorexia and severe thirst. He was prostrated, quite despondent and markedly dehydrated. The patient was moderately dyspneic, his temperature was 102° F. and the sclerae had become definitely icteric. The urine, which was dark brown, "prune juice" in color the day before, was now "port wine" in color. A blood count showed 16,150 white blood cells and a stained smear exhibited numerous immature cells, including normoblasts and many toxic neutrophiles. Sulfathiazole was discontinued. At this point, on the ninth day of his illness, the patient was removed to the hospital.

TABLE I

Hematological Data *

Day of Illness	1	6	8	9†	10	11	12	13	14†	15	16	18	23
Red blood cells (in millions)		4.30		3.69	2.78	2.84	2.10	3.19	2.95	2.54	2.46	2.35	2.29
Hemoglobin (per cent)		86	83	88	74	67	50	52	52	58	60	55	52
Normoblasts (per 100 w.b.c.)				5	0	0	0	0	2	½	0	1	0
Reticulocytes (per cent)				0.8		0.5	1.5		5.2	5.0	4.2	3.4	1.6
Platelets (in thousands)				180		150				570			
Plasma cells (per 100 w.b.c.)				0	0	1	1	1	2	0	0	0	0
White blood cells (in thousands)	10.3	7.5	16.1	17.5	15.0	22.0	27.6	33.5	29.6	25.5	24.2	14.6	13.4
Myelocytes (per cent)				0	0	0	5	0	6	5	1	1	0
Polymorphonuclears (non-segmented)	12	10	12	9	10	7	5	0	9	8	8	4	3
Polymorphonuclears (segmented)	71	72	75	75	68	73	64	58	55	54	55	63	69
Lymphocytes				11	11	8	14	33	21	27	29	16	22
Monocytes				3	2	7	9	8	5	3	3	4	2

* We are indebted to Dr. H. Maxwell Burry who furnished us with the laboratory data collected prior to the patient's admission to the hospital.

† On the ninth day there was 1 megaloblast per 200 white blood cells. On the fourteenth day there were 1 megaloblast and 1 myeloblast per 100 white blood cells.

The blood studies are recorded in detail in table 1. For the first few days after hospitalization the neutrophiles showed marked toxic changes; the cytoplasm contained toxic granules and the nuclei showed an unusual degree of edema. In many granulocytes the segmented nuclei were disconnected and took a solid, homogeneous, purplish-blue stain, resembling in appearance the nuclei of normoblasts. The red cells showed basophilic stippling and anisocytosis. A search for spheroid erythrocytes revealed none. The fragility test, clotting and bleeding times were normal. On the first and subsequent five hospital days the blood plasma contained free hemoglobin and methemoglobin on spectroscopic examination. The serum bilirubin, determined after removal of the hemoglobin, was 3.1 mg. per cent. The non-protein nitrogen was 67 mg. per cent. Sulfathiazole determinations on blood, urine and stool are recorded in table 2. The blood culture was sterile.

TABLE II

Sulfathiazole Determinations

Specimen	Day of Illness	Free Sulfathiazole	Total Sulfathiazole
Blood	9	4.0 mg. per cent	5.0 mg. per cent
Urine	9	28.6 mg. per cent	44.4 mg. per cent
Feces	9	100 mg. per gm.	160 mg. per gm.
Blood	11	0.6 mg. per cent	0.8 mg. per cent

Although the blood count on admission showed 3,690,000 red blood cells and 88 per cent hemoglobin, the patient was given a transfusion of 500 c.c. of whole citrated blood within an hour after admission. Another transfusion was given on the second hospital day and a third on the fifth day. Infusions of saline and 5 per cent glucose were given daily for the first four days, in an attempt to accelerate the rate of excretion of sulfathiazole. The urine output (2,250 c.c.) was about 50 per cent of the fluid intake on the first hospital day but gradually increased until it equaled the intake on the fourth day and thereafter. On the fifth hospital day the hemoglobin disappeared from the blood plasma and urine, the jaundice faded considerably and the patient felt markedly improved. As will be seen in figure 1, the peak in the reticulocyte and leukocyte rise was not reached until five and six days after the hemolytic crisis.

A second non-protein nitrogen determination of the blood done on the eighth hospital day showed a rise to 100 mg. per cent. Urinalysis of a casual specimen showed a specific gravity of 1.008, a trace of protein, a positive benzidine test and two to three red blood cells per high power field. The urea clearance was only 25 per cent of normal at a rate of urine flow above 2 c.c. per minute. No oliguria, anuria or hypertension developed at any time. Cholesterol determinations of the plasma on the thirteenth hospital day showed 167 mg. per cent of total cholesterol and 78 mg. per cent of cholesterol ester. A bromsulphalein excretion test showed a retention of only 10 per cent at the end of 30 minutes and complete disappearance of the dye from the serum by 60 minutes.

During the second week 1.2 grams of ferrous sulphate were given daily and later 15 units of liver extract were given intramuscularly for four successive days but no immediate rise was noted in the red blood cell count or the hemoglobin content.

The patient was discharged much improved on September 24, after remaining in the hospital for 14 days. He returned to work on October 14. A blood count done at this time showed 3,300,000 red blood cells and 68 per cent hemoglobin. The blood non-protein nitrogen was 38 mg. per cent.

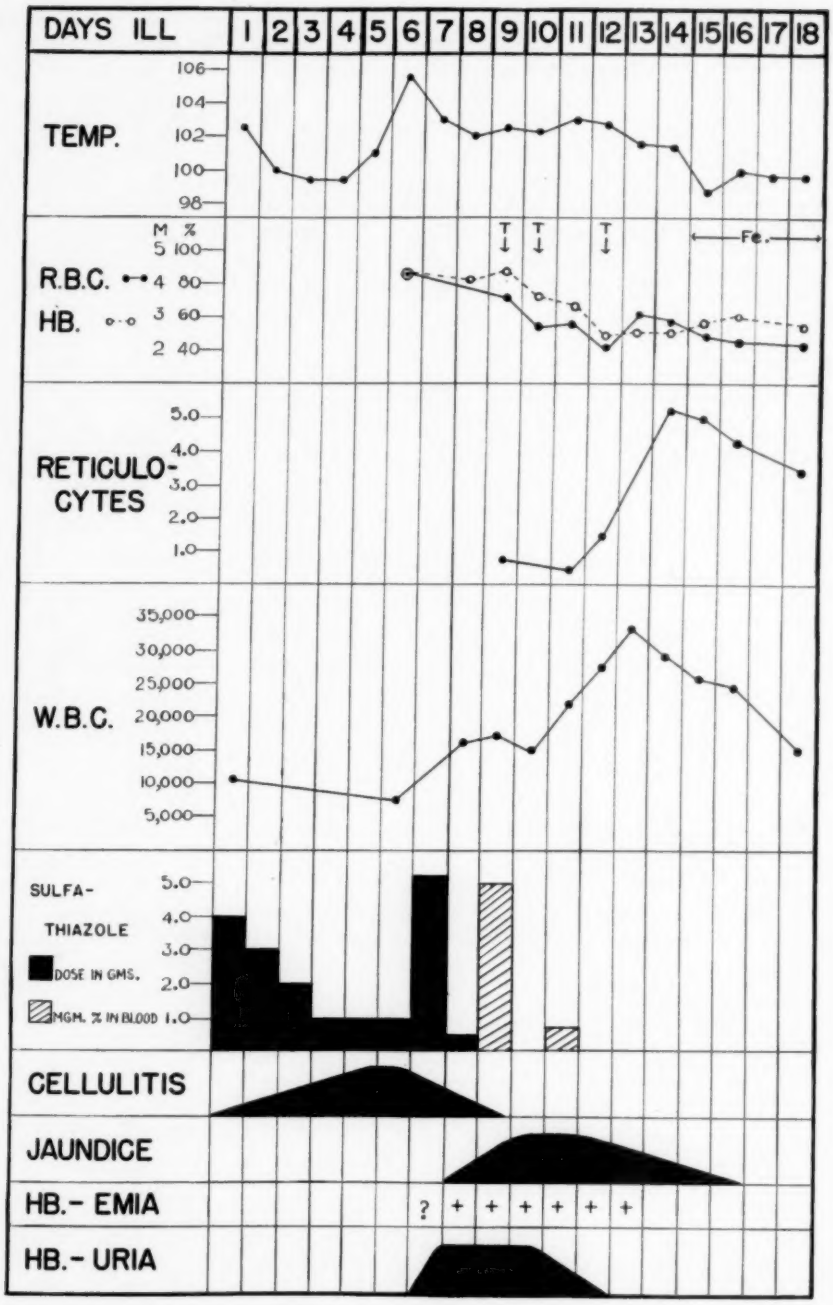

FIG. 1. The first eighteen days of the patient's illness. He was admitted to the hospital on the ninth day. Temp. = temperature (rectal); R.B.C. = red blood cells in millions per cu. mm.; Hb. = hemoglobin (Sahli) expressed in per cent; W.B.C. = white blood cells per cu. mm.; Hb.-emia = hemoglobinemia; Hb.-uria = hemoglobinuria; T = transfusion; Fe = ferrous sulphate.

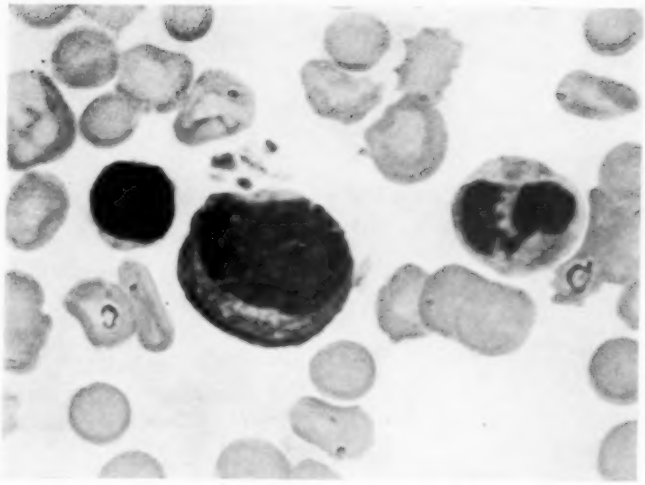

FIG. 2. Film of the peripheral blood on the fourteenth day of illness. A megaloblast is seen flanked on the left by a lymphocyte and on the right by a segmented neutrophile. This preparation showed one megaloblast per hundred white blood cells.

COMMENT

This patient was exposed to ultra-violet radiation for relatively long intervals while he was getting sulfathiazole. Ottenberg and Fox [13] have shown that when dilute solutions of sulfanilamide are exposed for brief periods to ultra-violet light a strong violet color develops. The nature of this chemical change was not described. We exposed sulfathiazole solutions of varying strengths to ultra-violet light and obtained no such color change. A pale, clear yellow color finally developed. Fox, Hogg and Ottenberg [14] had similar results. They believe that some of the sulfathiazole in the solution is changed upon radiation and that when hemoglobin is later exposed to this irradiated solution it is oxidized to methemoglobin. It is known that patients, when exposed to ultra-violet light while receiving either sulfanilamide or sulfapyridine, may develop severe dermatitis and mucous membrane lesions. However, we have encountered no report of such patients developing hemolytic anemia. Contrariwise, so far as we are aware, none of the patients in the reported cases of hemolytic anemia resulting from chemotherapy had been exposed to ultra-violet light. How much the combination of sulfathiazole and ultra-violet radiation contributed towards the development of hemolytic anemia in our patient is difficult to say. It is noteworthy that he developed no dermatitis or mucous membrane lesions and that his course closely resembled that of other patients with hemolytic anemia who had not received any radiation.

The slow excretion of sulfathiazole from the blood, the elevated nonprotein nitrogen and the markedly lowered urea clearance indicate that considerable impairment in renal function had taken place. This may have resulted either from the hemoglobinemia and hemoglobinuria,[15] or from the direct action of the drug on the renal parenchyma, or from both. The liver, on the other hand, seemed to have escaped any detectable damage. The ratio of cholesterol ester

to total cholesterol was well within normal limits as was also the interval in which the liver removed 90 per cent of bromsulphalein from the circulation.

Summary

A case of severe acute hemolytic anemia following the administration of 18 grams of sulfathiazole over a period of eight days is reported. The patient developed jaundice, hemoglobinemia, hemoglobinuria, azotemia and impaired renal function, besides the typical blood changes associated with a hemolytic crisis. Following prompt withdrawal of the drug and the institution of the generally accepted form of therapy, the patient recovered.

Addendum: Since this paper was submitted for publication, one of us (J. J. B.) encountered a second case of hemolytic anemia resulting from sulfathiazole. The patient was a 52 year old Greek male admitted to the Tuberculosis Service of Bellevue Hospital on March 20, 1941 complaining of fever, chills, cough and pain in the left anterior chest. He had had pulmonary tuberculosis of the right lower lobe for the past five years and had been receiving monthly refills of pneumothorax on that side. During this same period he was also known to have diabetes mellitus and was taking 22 units of protamine zinc insulin daily.

On admission he was found to have pneumococcus type III lobar pneumonia of the left lower lobe. He was also in moderately severe diabetic ketosis. He was treated for the latter condition with the necessary amounts of insulin and intravenous glucose and saline and his urine became free of glucose and acetone in 48 hours. His pneumonia was treated with sulfathiazole. Eight grams of the drug were given on March 21, six grams on March 22 and two grams on March 23, a total of 16 grams. On March 24 it was noted that he was markedly pale, his pulse rate was 120 and his temperature was 101.0° F. There was an icteric tint to his sclera. In 48 hours his red blood cell count fell from 4,100,000 to 2,100,000 and his hemoglobin from 12.0 gm. to 9.0 gm. per cent. The urine showed an abnormally high content of urobilin without bile. The icteric index of his blood was 17. On March 26 the differential count of his white blood cells showed 30 per cent polymorphonuclears, 29 per cent unsegmented granulocytes, 2 per cent metamyelocytes, 1.5 per cent eosinophiles, 0.5 per cent basophiles, 18 per cent lymphocytes and 19 per cent monocytes.

Two transfusions of whole blood totalling 700 c.c. were given on March 25 and March 26. The patient recovered from this hemolytic anemia as well as from his pneumonia and diabetic ketosis. On April 4 his red blood cell count was 3,800,000, hemoglobin 11.0 gm. per cent, icteric index 9 and his general condition was very good.

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AN INSTANCE OF CORONARY EMBOLISM IN SUBACUTE BACTERIAL ENDOCARDITIS *

By Harry Parks, M.D., *Atlanta, Georgia*

In recent literature on heart disease coronary thrombosis has occupied an increasingly important part of discussions on cardiac infarction. On the other hand, embolism of the coronary arteries with resultant cardiac infarction is infrequently mentioned. Up to 1933 Saphir [1] was able to find only 11 proved cases of this type, and to these he added three. During the last six years additional cases have been reported by Böger and Paradi,[2] Hoseason,[3] and by Cobo, Quirno, and del Rio.[4] The rare occurrence of coronary embolism is usually attributed to the anatomical situation of the coronary arteries. These vessels leave the aorta almost at right angles. Since the greatest velocity and bulk of the blood flow is in an upward direction, small particles leaving the left ventricle are likely to be swept far away from the mouth of the coronary arteries and do not often enter the coronary system. In the reported cases of coronary embolism, however, queer accidents have happened which have resulted in causing the lesion. In addition to coronary embolism caused by a vegetation set free from an active endocarditis or by a bit of clot breaking loose from an intramural thrombus, or by atheromatous material getting into the coronary vessels from the aorta, coronary embolism has been reported as due to fat, to air, to tumor cells or even to caseous tuberculous material.

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From the Robert Dawson Evans Memorial for Clinical Research and Preventive Medicine, Boston.

The following case is recorded to add one more case to the literature of subacute bacterial endocarditis in which death occurred as the result of coronary embolism.

Case Report

A 52 year old, white, Lithuanian housewife was admitted to the Robert Dawson Evans Memorial on September 20, 1938. She had been under the observation of various physicians for at least four years, consulting them because of progressive weakness, weight loss and pallor. Two years before entry she had weighed 91 kg. (200 pounds), gradually losing until she weighed only 56 kg. (123 pounds).

In 1935, three years before entry, Dr. Donato T. Scenna of Melrose, Mass., observed that she had an enlarged liver and spleen.

She entered the Robert Dawson Evans Memorial because of continued weakness. She admitted, too, that on exertion she now developed severe attacks of precordial pain or uncomfortable leg cramps.

She was poorly developed and nourished but she did not appear acutely ill. There was a peculiar reddish purple discoloration of the skin of the face, neck, and upper extremities, and marked pallor of the mucous membranes. No petechiae were observed. The pupils and pupillary reflexes were normal. The eye grounds had normal physiological cupping, and there were no hemorrhages or exudates. The heart on percussion appeared slightly enlarged. A soft precordial systolic murmur was noted, but no diastolic murmur was heard constantly. The blood pressure was 104 mm. Hg systolic and 60 mm. diastolic, and the pulse rate 80. The liver and spleen were greatly enlarged and firm in consistency. Several small axillary and inguinal lymph nodes were palpable. The remainder of the physical examination was not noteworthy.

Significant laboratory findings consisted of a well-marked hypochromic anemia; a normal white blood count and differential smear; a moderately low platelet count; a tendency to fixation of specific gravity of the urine; microscopic hematuria; a diminished phenolsulphonphthalein excretion; an elevated blood non-protein nitrogen level; hypoproteinemia with reversal of the albumin-globulin ratio; and achlorhydria to histamine stimulation. The blood Wassermann reaction was negative. Agglutination tests for typhoid, paratyphoid A and B and undulant fever were negative. A single blood culture showed no growth at the end of seven days. Urine specimens removed from each kidney were sterile on culture and microscopic examination. The venous pressure was 90 mm. of water, and the circulation time by the Decholin taste method was 12 seconds. The basal metabolic rate was not elevated. An electrocardiogram made shortly after entry to the hospital showed regular sinus rhythm and normal P R intervals. Roentgen-ray and fluoroscopic examinations of the heart demonstrated calcification in the region of the aortic valve leaflets. Other roentgen-ray studies were not remarkable except for the incidental discovery of gall-stones.

The behavior of the patient's temperature was of interest. During the first three weeks of her stay in the hospital she was fever-free. During the following weeks of her illness she developed a low intermittent fever characterized by three or four days of normal temperature alternating with equal periods when the temperature rose to 99° or 100° F. During such febrile episodes there was no tachycardia, and electrocardiographic tracings remained normal.

No significant changes in symptoms or signs occurred until December 19, two and one half days before her death, and three months after her entry to the hospital. At about 10 o'clock in the evening, while lying in bed, she developed suddenly a violent nausea which was soon followed by sharp epigastric pain referred upward behind the sternum, but not radiating to the neck or arms. The pain was accompanied by vomiting. Approximately five hours after the onset of this attack, the temperature was 98° F., and the pulse rate was 90. There was a rise in blood pressure to 140 mm. Hg systolic and 85 mm. diastolic. Physical examination shortly after the

attack began revealed striking changes in the character of the heart sounds. There was now a loud blowing diastolic murmur audible over the base of the heart, loudest over the aortic area, and transmitted downwards toward the left sternal border where it was easily heard over the second and third intercostal spaces. The murmur in the apical region did not change. Marked epigastric tenderness was present which was thought to be due to enlargement of the liver. The lungs were clear. There was no edema. An electrocardiogram, made 12 hours after the attack began, showed changes in the precordial lead suggestive of myocardial infarction. This diagnosis was borne out subsequently by tracings taken at later intervals.

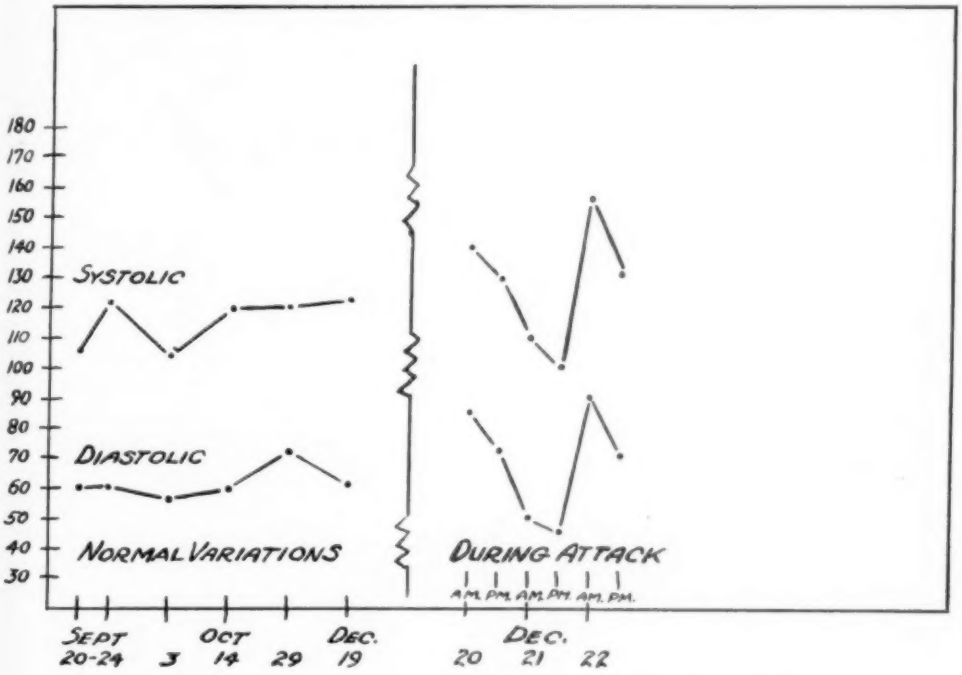


FIG. 1. The blood pressure level in coronary thrombosis from embolism.

During the first 48 hours after the onset of the cardiac infarction the temperature ranged from 99° to 100° F., and the pulse rate from 100 to 120. The respiratory rate rose to 28. The blood pressure soon fell to 100 mm. Hg systolic and 45 mm. diastolic. The patient grew worse rapidly. On the third day, 54 hours after the onset of pain, her temperature fell suddenly to 96° F.; she developed diffuse cyanosis and marked air hunger. Curiously, the blood pressure now rose temporarily to 156 mm. Hg systolic and 90 mm. diastolic, although the heart sounds were distant and of very poor quality. The abdomen became distended. A little later the blood pressure again fell to 120 mm. Hg systolic and 70 mm. diastolic, and the heart began to fail rapidly; râles at the lung bases developed, and the neck veins became distended. A few hours before death the blood non-protein nitrogen concentration had risen to 100 mg. per cent and the CO_2 combining power had fallen to 11 vol. per cent.

At necropsy, the important findings concerned the heart, spleen and kidney. The pericardial sac contained about 15 c.c. of thick, flocculent, fibrino-purulent material. Culture of this fluid was negative. The visceral and parietal pericardial surfaces were smooth and glistening and showed only slight capillary engorgement. The heart

weighed 410 gm. The anterior descending branch of the left coronary artery in its terminal 4 cm. stood out sharply as a dense, occluded, cord-like mass. The outer two-thirds of the left ventricular apex and the interventricular wall were soft and friable, and obviously infarcted. On the right posterior cusp of the aortic valve were soft, friable vegetations, longitudinally arranged, and measuring approximately 7 mm. in length and 3 mm. in width. Near the commissure of this leaflet was a small plaque of calcification 4 mm. in diameter. The anterior surface of the left posterior valve was almost completely covered by soft, finger-like vegetations composed of fibrinous material. Extending outwards from the posterior surface of the cusp into this ma-

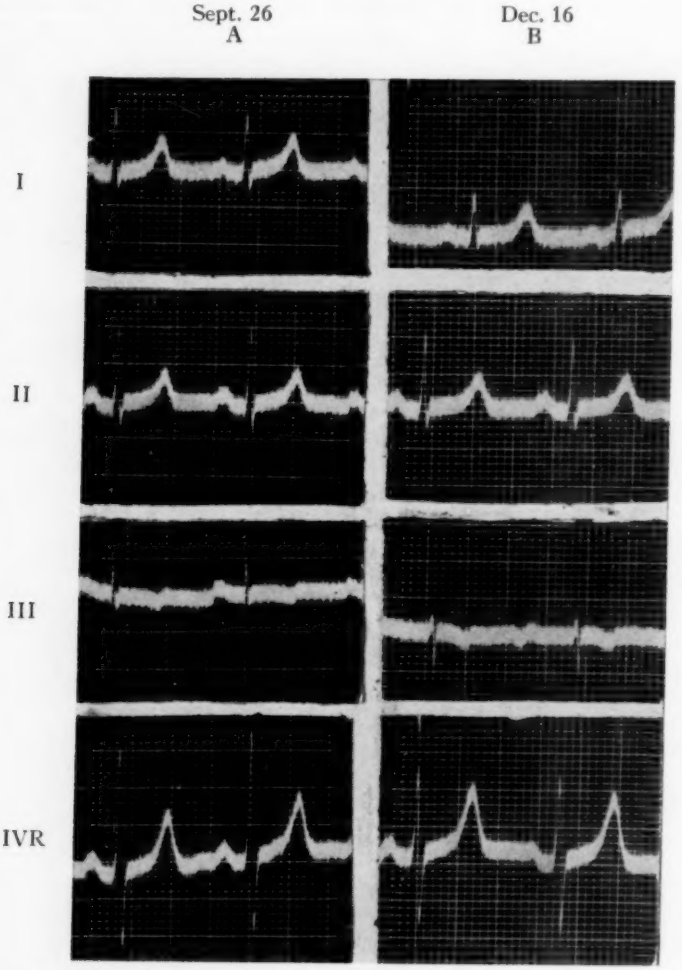


FIG. 2. *A* and *B*, electrocardiograms made before the onset of coronary embolism show normal sinus rhythm and ventricular rate of 80. *C*, a tracing made 12 hours after the onset of coronary embolism shows decrease in voltage of QRS complexes in all the leads, nearly complete disappearance of R_4, flattening of T_1, changes in direction of T_3 from negative to positive, high take-off of ST_4 and sinus tachycardia with ventricular rate of 120. *D*, a tracing made four hours later shows little change except decrease in depth of S_4. The ventricular rate is 140. *E*, a tracing made 38 hours after the onset of coronary embolism shows a slurred S_1 and Q_3, flattening of T_1, isoelectric T_2, inversion of T_3, decrease in take-off of ST_4 with inversion of T_4, upward convexity of ST_4 and sinus tachycardia with ventricular rate of 120.

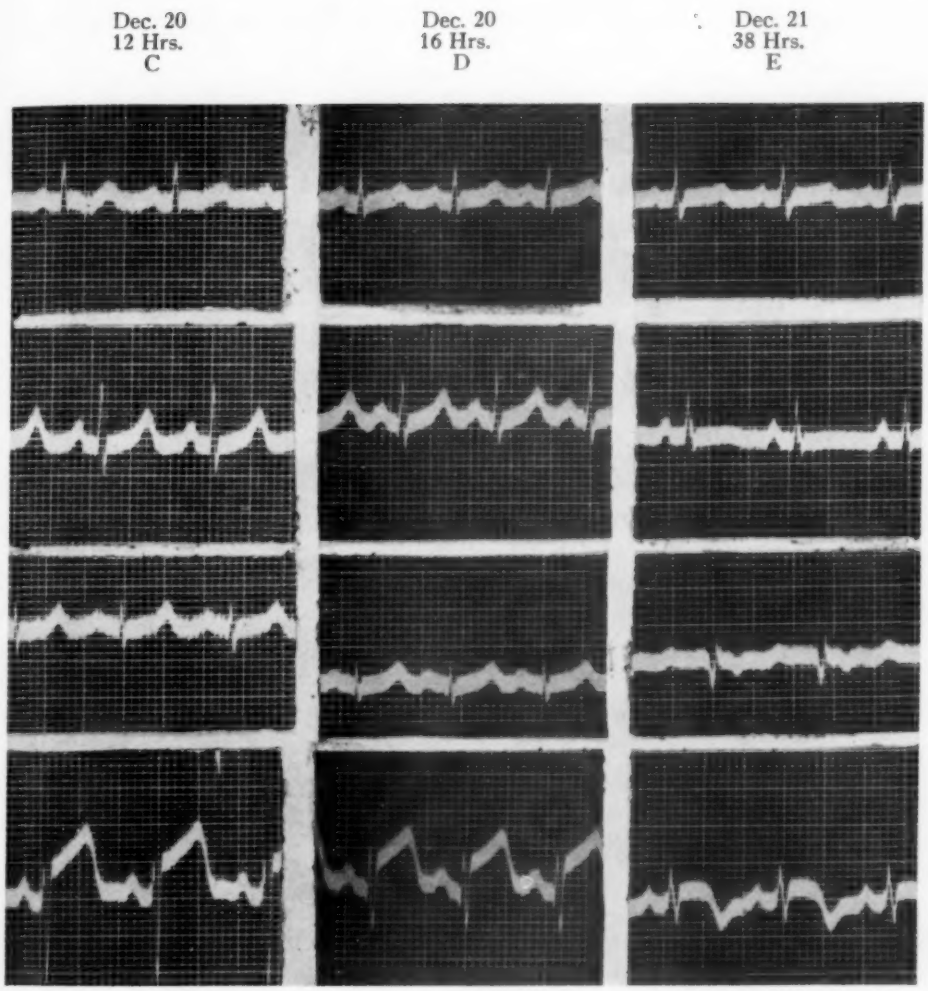


FIG. 2 (*continued*)

terial and forming a cup-like entity 4 mm. in diameter was a mycotic aneurysm of the valve leaflet. The anterior valve leaflet presented a similar excavation measuring 5 mm. in diameter; its outer anterior surface also was covered with necrotic fibrinous material. The pulmonary and tricuspid valves were entirely normal. At the base of the mitral valve there were atheromatous deposits and beginning calcification of the mitral ring.

The orifices of the coronary arteries were normally placed and widely patent. The immediately adjacent intima showed well-defined early vegetative lesions which were so minute that they were discernible only with the aid of a hand lens. These were in no way occlusive in nature. The coronary arteries on gross examination were remarkably free from any atheromatous lesions or evidence of fibrosis. The anterior descending branch of the left coronary artery at a point approximately 4 cm. from the apex was occluded by a firm, dry, somewhat friable embolus measuring approximately 1 cm. in length. This was partially adherent to the vessel wall. On either

side of the embolus the vessel was free of any obstruction, and the vessel wall appeared normal.

Microscopic examination of a section through the aortic valve cusp at one of the pouch-like areas showed a well-defined mycotic aneurysm within which was a large amount of partially organized blood-clot. In and about this were many colonies of

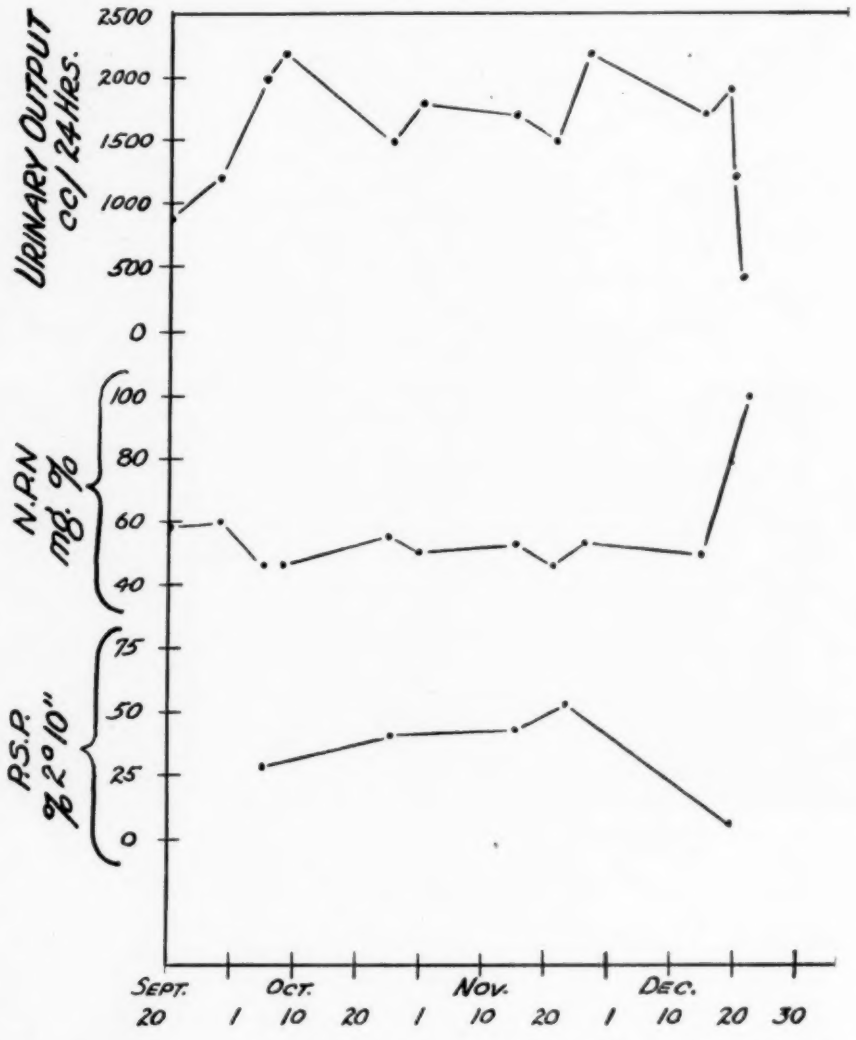


FIG. 3. The blood non-protein nitrogen, the urinary output, and phenolsulphonphthalein output in coronary embolism.

streptococci. The larger coronaries showed only moderate fibrous and hyaline thickening of the intima. In the occluded area there was a thrombus which appeared to have developed from an embolus set free from one of the vegetations on the aortic valve leaflets.

The aorta showed rare small atheromatous plaques throughout its entire course

with one area of calcification just above its bifurcation. There was no evidence of thromboses or emboli in any of the larger vessels.

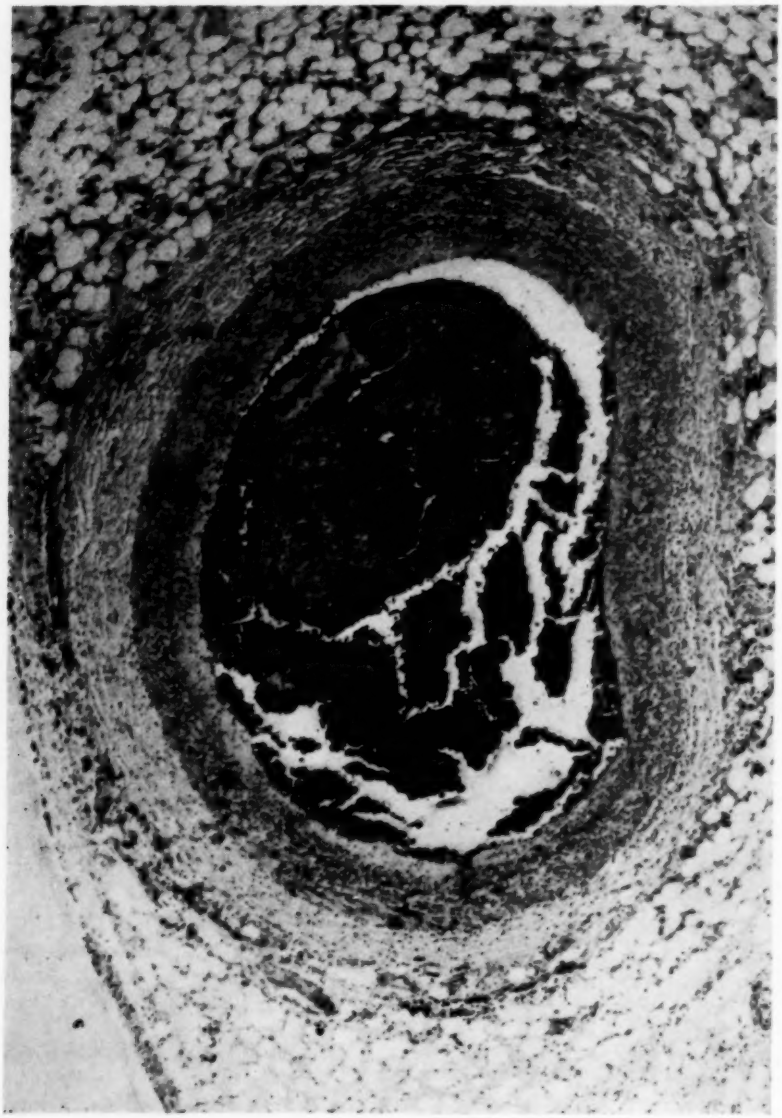
The spleen weighed 780 gm. and was dark reddish to purplish-gray in color. In the upper pole was an old infarct which was roughly 4 cm. in diameter.

FIG. 4. Photograph of the heart showing the cusps of the aortic valve with vegetations. The retracted cusp on the right shows vegetations on the upper surface of the leaflet and a mycotic aneurysm.

The kidneys together weighed 290 gm. The renal cortex was stippled with many minute, punctate, bright red dots. On histological study many of the glomeruli showed embolic glomerular lesions; the tubules contained a large number of blood casts, hyaline and granular debris.

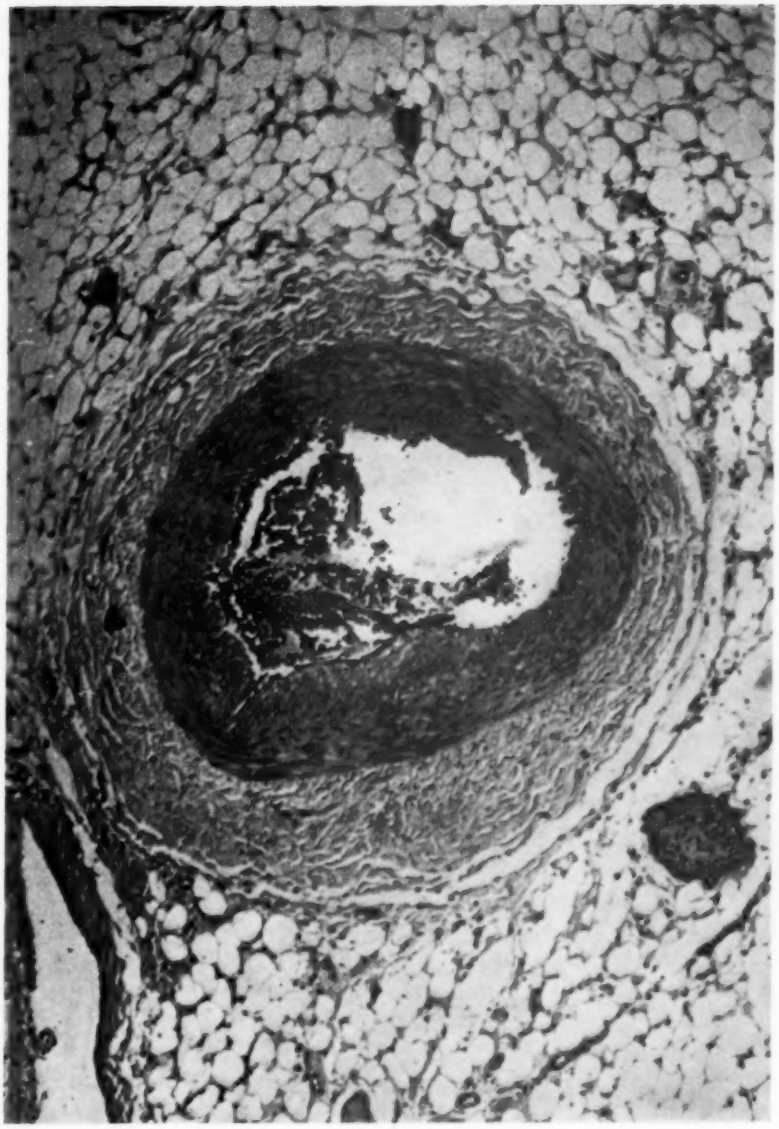
Virchow [5] is given credit for having first described coronary embolism. In 1856 he reported the case of a 27 year old girl who had endocarditis of the mitral valve with emboli to the coronary arteries. Saphir, as has been already

mentioned, in 1933 reviewed the literature of coronary embolism up to that time and found only 11 acceptable cases. In these, embolism was found to occur most frequently in the left coronary artery or its branches; and sudden death practically always resulted. The youngest patient noted by him was a case of Rolleston's, a 17 year old boy who died suddenly from an embolus in the de-



A

FIG. 5. The coronary artery. A. Photomicrograph of the artery approximately 4 cm. from the apex. The embolus shows no organization. There is early neutrophilic infiltration of the vessel wall. × 50. B. The same vessel 1 cm. lower. × 50. The vessel wall appears normal.



B

FIG. 5 (*continued*)

scending branch of the left coronary artery which originated from a thrombus in the left ventricle.

Since Saphir's review additional reports of coronary embolism have appeared occasionally. Hoseason reported a 36 year old patient who collapsed in the street while walking to work. At necropsy, he was found to have left ventricular hypertrophy. The aortic valves were calcified. On the right posterior aortic cusp a thrombus was loosely attached to an ulcerated area over a calcified nodule.

One-half inch along the right coronary artery was a small particle of vegetation which was thought to have originated from the ulcerated valve cusp. Böger and Paradi reported the case of an 18 year old woman with subacute bacterial endocarditis. She suddenly developed intensive oppression and chest pain, tachycardia, weak pulse, poor heart sounds, labored respiration and cyanosis, and died in a few minutes. Necropsy demonstrated an endocarditis of the mitral valve with a fresh embolus in the left coronary artery. The ventricle did not show infarction, apparently because of the suddenness of death.

Cobo, Quirno and del Rio described the case of a woman 36 years old who developed griping precordial pain after getting up quickly from the table. The pain increased in intensity, and soon she complained of palpitation and a sense of impending death. Physical examination showed a soft presystolic murmur in the mitral area. There were no thrills. Electrocardiographic tracings gave findings characteristic of coronary occlusion. On the second day of the patient's illness, she developed signs of frank cardiac insufficiency and died on the third day after the onset of the attack. Necropsy revealed several small yellowish-white vegetations on the mitral valve. These were friable and varied in size. The left coronary artery and its branches were normal. In the right coronary artery was a small embolus firmly adherent to the wall of the vessel. This was thought to resemble in character the vegetations on the mitral valve.

Our case appears unusual in several ways. In the first place the latency of the endocarditis was striking. The patient had been seen in various clinics during her prolonged illness and always her marked anemia and huge spleen attracted attention. No one paid any particular attention to the cardiac and renal findings.

In the second place the behavior of the blood pressure at the time of the coronary embolism is worth emphasizing. It has already been pointed out by Fitz,[6] Wood and Wolferth,[7] and others that an initial rise followed by a fall in blood pressure may take place in acute occlusive coronary lesions. In our case an initial rise, then a fall, and finally a second rise and fall in blood pressure occurred, the highest reading being obtained shortly before death.

The marked terminal rise in the blood non-protein nitrogen level which was observed in our case has been noted in other cases by Steinberg,[8] and by Jeghers and Bakst.[9] Presumably the rise was due to dehydration, oliguria, and other extrarenal factors superimposed on an already existing nephritis. As in other cases the rapid accumulation of non-protein nitrogen in the blood was an ominous sign.

On the whole the case is reported as representing an example of a chronic form of subacute bacterial endocarditis with a notable splenomegaly, anemia, and characteristic pathologic findings in heart and kidney. Death resulted from cardiac infarction due, we believe, to coronary embolism. Coronary embolism as a complication of subacute bacterial endocarditis occurs infrequently, but when it does occur it may induce a striking sequence of clinical events.

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SPONTANEOUS HEMOPNEUMOTHORAX; REPORT OF A CASE *

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Spontaneous hemopneumothorax, judging by the number of case reports, is a rare condition. Hopkins,[1] reviewing the literature in 1937, found 46 cases reported since 1900. This entity apparently represents a spontaneous pneumothorax in which some unusual condition is present to give rise to bleeding into the pleural cavity. It must be distinguished from traumatic hemopneumothorax and from the effusion of bloodstained serum occasionally seen in malignant growths of the lung and pleura.

Our patient presented a classical example of spontaneous hemopneumothorax. Although a total of over 1400 cubic centimeters of blood was removed from his pleural cavity, he made a reasonably uneventful recovery. Because of the known value of sulfanilamide in keeping stored blood sterile, this drug was given the patient by mouth and may have assisted in preventing infection of the blood present in the pleural cavity. We were interested to observe the correlation between the sedimentation rate and the amount of blood remaining in the pleural cavity, shown by serial sedimentation rate determinations and chest roentgenograms taken concomitantly.

Case Report

The patient, E. C., was first seen on March 20, 1940 with the history that eight days previously he had experienced the sudden onset of an excruciating pain in the right side of the chest while at school. He felt quite weak and was taken home. Upon reaching home he fainted. He revived quickly but was dyspneic, orthopneic, and developed a dry hacking cough. He remained in bed. His mother stated that when moving him she could hear a splashing sound. He complained of a frontal headache which was constant. Epistaxis occurred twice during the eight day period. Fever ranging between 100° and 102° F. was present.

The patient's previous health had been good. He had been wrestling about

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two months previous to the above event and had experienced a pain low in the right chest. This pain was not severe and had disappeared after several weeks. A careful physical examination about a week before the onset of the illness was negative. The family history revealed that the patient's aunt had had tuberculosis.

Physical examination revealed a pale asthenic youth who appeared quite ill. Dyspnea was marked and the patient was unable to stand for any time without support. The temperature was 100.5° F. The area representing the base of the right lung was flat to percussion and the interspaces on the right side of the chest were full. The apex beat was 4.5 centimeters to the left of the nipple line. No breath sounds were audible over the lower two-thirds of the right lung. Fluoroscopic examination revealed complete density of the lower three-fourths of the right chest cavity with a horizontal fluid level indicating pneumothorax. The red blood count was 4,460,000,

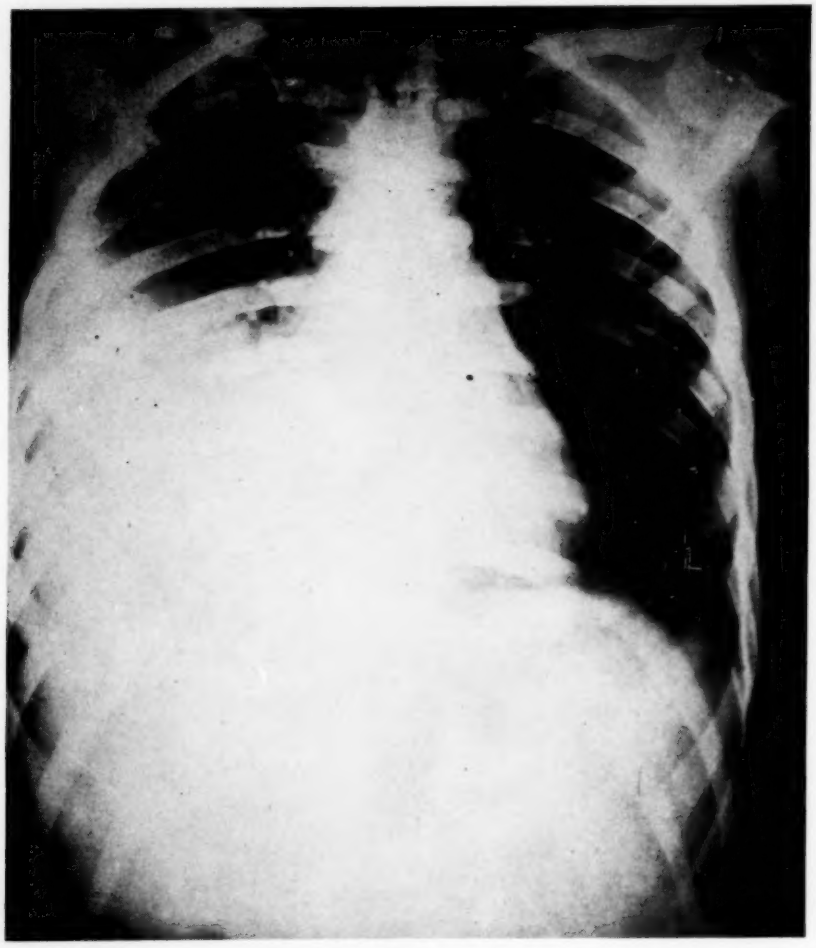

FIG. 1. Anteroposterior roentgenographic view of the chest taken in the recumbent position with the use of a Potter-Bucky diaphragm on April 15. Shows a marked effusion in the right pleural cavity extending upward to the level of the third interspace. The sedimentation rate at this time was 45 millimeters in 1 hour.

the white count 25,600, and the hemoglobin 65 per cent. Wassermann and Kahn tests were negative.

Under local anesthesia thoracentesis was performed in the seventh interspace posteriorly on the right side. Pure blood was obtained. The needle was withdrawn and reinserted in a different location to rule out the possibility of venepuncture. Blood was obtained in this area also. About 450 c.c. of non-clotting blood were then

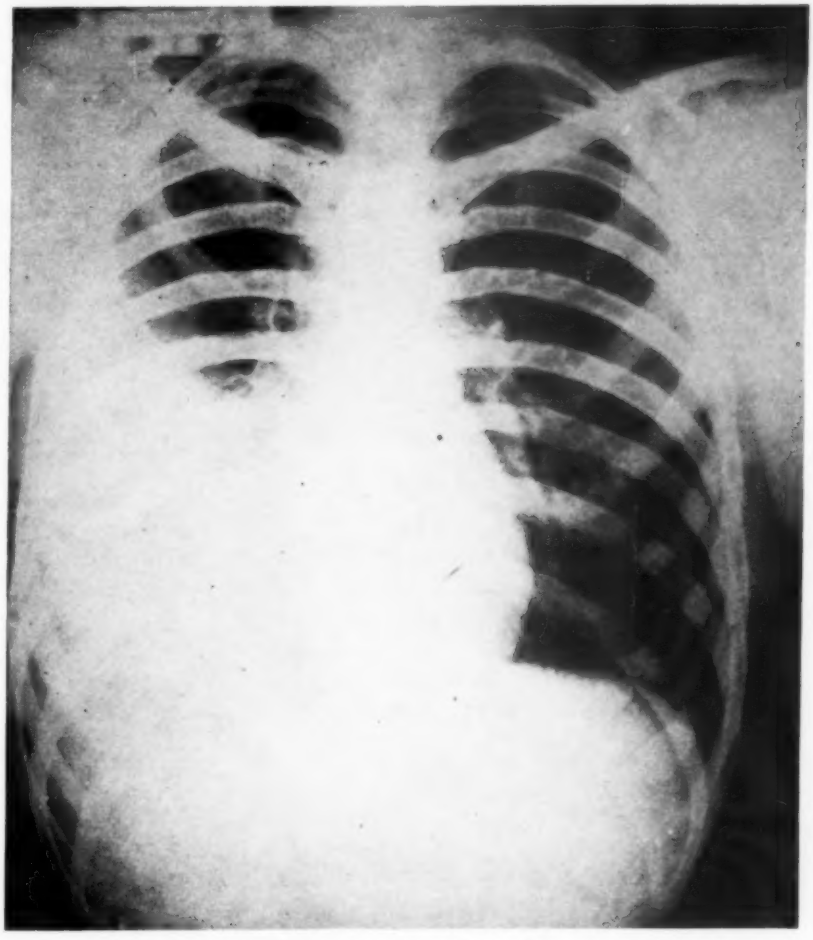

FIG. 2. Chest roentgenogram taken on April 26 showing partial clearing of the right pleural cavity and reduction of the density to the level of the fifth rib. The sedimentation rate at this time was 23 millimeters in 1 hour.

removed by aspiration. Air was found to be present above the effusion area. The patient experienced some relief from dyspnea but was extremely weak. Shock treatment was given. The fluid removed from the pleural cavity appeared like normal blood except that it did not clot. The hemoglobin content was 65 per cent, exactly that of the blood specimen obtained from the patient's finger.

During the following three weeks the patient made excellent progress. Dyspnea and orthopnea were markedly relieved following the tap. Sulfanilamide was admin-

istered in an effort to prevent infection of the blood remaining in the pleural cavity. However, the patient continued to run a low grade fever for two weeks. Hematinics were administered and the red cell count rose. The white count decreased.

On April 1 fluoroscopy revealed a basal shadow on the right but no fluid level. The temperature was 98.6° F., and the hemoglobin 80 per cent. Thoracentesis was performed, and 1050 c.c. of non-clotting blood were withdrawn. The patient stood the

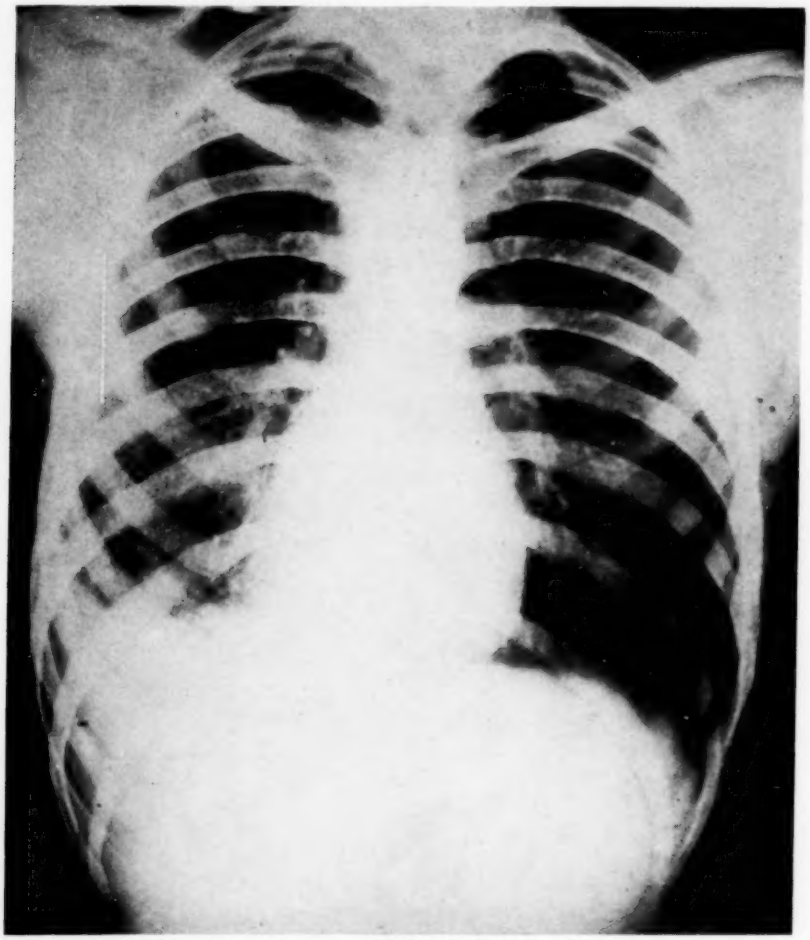

FIG. 3. Chest roentgenogram taken on May 20 revealing practically complete evacuation of the effusion. Both lung fields appear normal but there is fixation of the right leaf of the diaphragm. The sedimentation rate was 5 millimeters in 1 hour (normal).

procedure well. Fluoroscopy following the tap revealed persistence of the shadow over the right lung base but lessening of its density. Continued improvement followed the procedure.

On April 15 a chest roentgenogram, taken in the recumbent position with the use of a Potter-Bucky diaphragm, revealed marked effusion in the right pleural cavity to the level of the third interspace (figure 1). The sedimentation rate was 45 millimeters in one hour. The urine at this time was found to contain albumin.

Bence-Jones protein was absent and the glucose test and microscopic examination were negative.

A chest roentgenogram on April 29 revealed clearing of the right pleural cavity and reduction of the density to the level of the fifth rib. The left thoracic cavity was normal in appearance (figure 2). The sedimentation rate was 23 millimeters in one hour. The hemoglobin at this time was 80 per cent.

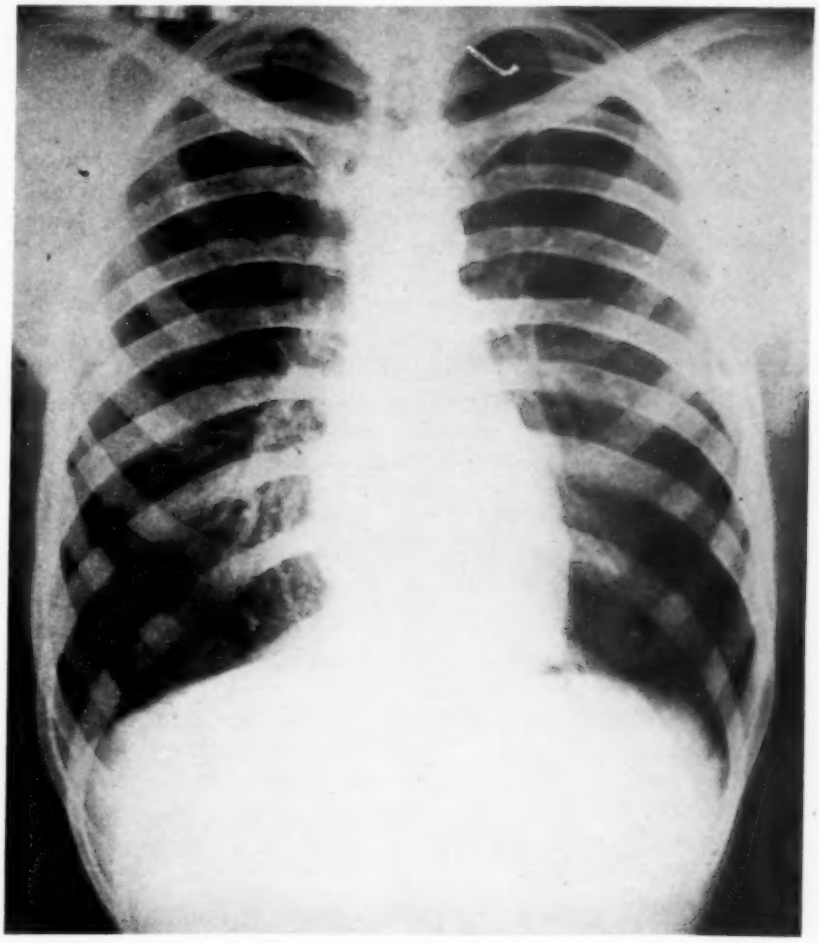

FIG. 4. Chest roentgenogram taken on August 12 showing complete clearing of the right costo-phrenic angle and normal lung fields.

On May 20 a chest roentgenogram revealed practically complete evacuation of the fluid. Both lung fields appeared normal, but there was fixation of the right leaf of the diaphragm (figure 3). The sedimentation rate was 5 millimeters in one hour.

Repeated fluoroscopic examinations in the succeeding weeks revealed gradual clearing of the right costo-phrenic angle. On August 12 the right leaf of the diaphragm showed normal excursion, complete clearing of the right costo-phrenic angle, and normal lung fields (figure 4). At this time the patient stated that he was feeling very well and had no complaints.

Comment

Hemopneumothorax may occur as a result of trauma or it may occur as a complication during artificial pneumothorax, as reported by Hurst and Epstein.[2] These types of hemopneumothorax are not to be classed as spontaneous. Frey[3] classified as spontaneous those cases in which there was a lack of a definite cause, such as demonstrable disease or trauma.

The majority of cases of spontaneous hemopneumothorax occur in individuals previously in good health. In an analysis of 17 cases Jones and Gilbert[4] found the age limits to be 17 and 44 years. In over half of the cases the condition had occurred in the third decade. All of these patients were males. As Hopkins[1] points out, the disproportionate incidence in males is difficult to explain. If the condition is due to developmental defects, he reasons, these should occur in females as frequently as in males. If latent tuberculosis were a factor the incidence should be higher in women. If physical activity were important the increasing participation of women in strenuous sports and occupations should cause an increasing incidence in females. This, apparently, has not occurred.

As regards the mechanism of production of spontaneous hemopneumothorax, the consensus is that it probably consists of the rupture of an emphysematous air vesicle lying beneath the pleura, followed by the tearing of pleural adhesions containing blood vessels.

Birch[5] reported the findings at postmortem examination in a fatal case of spontaneous hemopneumothorax as follows: "The right pleural cavity contained several pints of fluid blood and some air. There was a minute tuberculous cavity at the apex of the right lung, but it had not ruptured. There were no emphysematous blebs. On the anterior surface of the right upper lobe there was a roughened area of pleura and bleeding and escape of air had apparently originated here, but there was no gross macroscopic change. Apart from the minute cavity there was no other evidence of tuberculosis in the right lung. The other lung and the rest of the body were quite normal." Birch[5] mentions the findings in five previously autopsied cases: In the first a torn adhesion to an emphysematous bulla was found. There was no evidence of tuberculosis. In the second the cause of bleeding was not ascertained. In the third, torn adhesions to subpleural blebs were found, associated with a puckered tuberculosis scar. In the fourth case a torn emphysematous bleb was present at the apex, the edges of the tear being covered with coagulated blood. There was no evidence elsewhere in the lungs of tuberculosis or emphysema. In the fifth case a ruptured bulla was found, but there was no evidence of tuberculosis.

In a case described by Housden and Piggot[6] ". . . necropsy revealed the presence of a firm pleural adhesion attached to an emphysematous cavity at the apex of the left lung. The adhesion appeared to have been torn away from the chest wall during life, and it seems quite possible that it was from the torn adhesion that bleeding took place."

The symptomatology of spontaneous hemopneumothorax is that of spontaneous pneumothorax combined with the symptoms of hemorrhage and of pleural effusion. The clinical picture in a given case will depend upon the relative parts which these factors play. As Head[7] states, the loss of blood is both complicated and aggravated by the collapse of the lung and by the resultant

pressure on the heart and great veins. The initial pain may occur while the patient is at rest or it may follow slight exertion. It is usually localized at first but later may involve the entire side of the chest or even the abdomen. Thus Milhorat [8] reported a case of spontaneous hemopneumothorax in which the abdominal signs simulated those of an acute surgical abdomen. In reviewing the literature Hopkins [1] found that in many cases there has been noted a second sharp attack of pain occurring from a few hours to several days after the original onset of pain. This has been followed by signs of effusion. If the bleeding is slow, signs of hemorrhage may be mild or may never appear. In several cases blood has been discovered as an incidental finding.

Treatment will vary considerably with the individual case. If the amount of blood in the pleural cavity is slight, thoracentesis may be delayed. If fluid is present in such large amounts as to cause pressure symptoms, however, it should be withdrawn. In view of the possibility that calcification of the pleura or other complications may result, should a considerable quantity of blood be allowed to remain in the pleural cavity, it would seem wise to prevent such an occurrence by thoracentesis as indicated. However, as Louria [9] aptly states, complete drainage of the pleural cavity or the reduction of the intrapleural pressure to a distinctly negative level may result in further bleeding or in the opening up of a partly closed bronchopleural fistulous tract.

It is of obvious importance in the management of a case of hemopneumothorax to determine whether or not the hemorrhage is progressing. Korol [10] suggests that if the aspirating needle is blocked by clots, or if the aspirated blood clots in the basin, one may infer that hemorrhage continues. As the cell count of the fluid varies with the site of puncture and the position of the patient, serial blood counts on aspirated fluid may be of no help in determining the persistence of hemorrhage. Of obvious importance are frequent blood counts on capillary blood, blood pressure examinations, and serial chest roentgenograms or fluoroscopic examinations. We found a definite correlation between the amount of blood present in the pleural cavity as revealed by chest roentgenograms and the sedimentation rate (figures 1 to 4).

Korol [10] suggests that in cases in which bleeding continues and there is danger of exsanguination, a thoracoscope should be introduced into the pleural cavity and the bleeding vessel cauterized, after aspiration of the pleural contents.

Although recurrence of spontaneous pneumothorax is well known, there are no recorded cases of recurrent spontaneous hemopneumothorax. It seems likely that pleural adhesions following the presence of blood in the cavity make further collapse and bleeding impossible.

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SULFONAMIDES AND HEPARIN IN THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS *

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THE sulfonamides and heparin have been among the most recent forms of therapy in subacute bacterial endocarditis. Concerning the value of the sulfonamides there are widely divergent opinions. Some are to the effect that they are of doubtful or no value, others that recoveries may be definitely ascribed to their usage.[1, 2, 3, 4, 5, 6, 16] Concerning heparin in conjunction with sulfapyridine, no optimistic conclusions have been expressed since the sanguine preliminary report by Kelson and White.[7]

A consideration of factors involved in subacute bacterial endocarditis clarifies the reasons advanced for the employment of heparin and sulfonamide compounds, and also suggests explanations for the results.

Streptococcus viridans appears to be not a species but a heterogeneous group of cocci widely dissimilar in many ways. Some strains are resistant and others susceptible to the sulfonamides.[8] It has been suggested [8] that it might be worth while, before embarking on a course of treatment, to determine by cultural methods the degree of susceptibility of the patient's streptococcus to the action of sulfonamides.

The bacteria accumulate within the valve cusp's margin where no blood vessels penetrate, and so are safe from attack by leukocytes from within (leukocytes being the chief agents of destruction of the *Streptococcus viridans*) and secure from antibodies and chemotherapeutic substances in the blood bathing the valve from without. Should the bacteria migrate toward the valve base where blood vessels penetrate, they face destruction by leukocytes. Should they erupt through the valve edge, they are exposed to the blood stream or swept into it, and may be destroyed. Fibrin and platelets are deposited at the damaged site, providing for the remaining bacteria an ideal culture medium and a barrier against the blood stream that is absolutely impenetrable.[9] Spreading outward, at the vegetation's base, there is almost always a reparative fibrosis. Should these processes of defense and healing outstrip the processes of bacterial multiplication and thrombotic formation, healing would ensue.

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To aid these natural processes, the sulfonamides have been employed for their bacteriostatic and possible bactericidal action. The theory has been advanced that, during sulfonamide administration, "all of the preëxisting thrombi should become organized into fibrous scar tissue, while all newly formed thrombi in a patient under active treatment will be impregnated with the drug. Thus conditions will tend to become less and less favorable for growth of the organism if an effectual drug is taken continuously over a long period of time." [9] It is not yet clear which of the sulfonamide drugs, if any, is preferable, so that in vitro studies of the susceptibility of a patient's organism to the different sulfonamides would be helpful in selecting a drug.

Heparin was added on the theory that it would inhibit fibrin formation [10] and so "restrict the nidus and culture medium for bacterial growth, prevent embolism from the freeing of fresh thrombus, and check the growth of the vegetations so that proliferating fibroblasts may fill in the areas thus limited." [7]

According to the method of Kelson and White, after one week of sulfapyridine therapy, heparin was administered intravenously for 14 days, a venous clotting time of approximately one hour being maintained. Sulfapyridine was given continuously for a total of four weeks.

That heparin actually prevents the deposition of fibrin and platelets on a damaged valve has not been proved, although it has been effective in preventing thrombosis in experimental animals. However prolonged the bleeding time, it is probable that thrombus formation continues, although at decreased speed. A case treated with heparin alone died on the fourteenth day of treatment. Microscopically, the valve differed in no way from those seen in untreated cases. Bacterial vegetations were covered with fibrin thrombus, much of the fibrin appearing to be of recent deposition.[11]

Success of the combined treatment would depend on several concurrent circumstances: (1) a bacteria susceptible, when accessible, to the drug employed, and not present in overwhelming numbers and virulence; (2) a sufficiently active reparative fibrosis; (3) concentrations of the inaccessible bacteria within thrombi or valve substance not too large to withstand the leukocytic and fibroblastic activity; (4) foci of inaccessible bacteria limited to areas small enough to be wiped out by leukocytes and fibrosis during the period of treatment.

Theoretically, an ideal combination of these circumstances should lead to a cure.

Clinically, it would seem that when sulfanilamide or sulfapyridine is introduced into the body the accessible organisms, if susceptible, are rather quickly inhibited. This produces objective or subjective improvement (decrease in toxicity, lowering of temperature, sterilizing of blood cultures) for periods of a few days to weeks depending upon the virulence of the organisms, the number of foci, and the speed of multiplication.

However, if the inaccessible organisms not reached by the drug are not destroyed by the defensive and reparative processes within the valve substance, they continue to multiply, with gradual resumption of previous clinical signs and symptoms. In addition to the effect of these hidden and protected organisms, the streptococcus may develop an immunity to the action of the drug, so that even larger doses become ineffectual.

The following case was treated with heparin, sulfapyridine, and sulfathiazole.

Case Report

White male, aged 44 years, entered the medical service July 9, 1941, with a six months' fever, joint pains, and loss of strength.

Past history was non-contributory, except for scarlet fever at fourteen.

In January, 1941, he had "influenza" for four days, from which he apparently recovered. Two weeks later, he had pain and swelling of the left jaw for five days. During the month of February, he grew progressively weaker and had aching joints. A blood culture on February 26 was positive for a streptococcus, and he was given sulfapyridine until May 1. Although weak, he felt well, and returned to work. In June, he felt worse and took to bed. He was given sulfapyridine for one month, but blood culture remained positive. He returned to work for 10 days and then entered the hospital.

He was well developed, ambulatory, and did not appear acutely ill. There was no evidence of petechiae in the skin, mucous membranes, or fundi. Teeth were in good condition with no marginal gum infection. The throat was clean. Heart was normal in size, with a fairly loud systolic murmur in the mitral area. No diastolic murmur was heard, and the rhythm was regular. Liver and spleen were not palpable.

Course: Blood cultures were positive for *Streptococcus viridans* on July 9, 13, 16. On July 19, sulfathiazole was begun, and continued to August 20. Blood concentrations of free sulfathiazole ranged between 5 and 7.9 mg. per cent. Blood cultures: July 24, no growth; July 30, no growth; August 5, heavy growth; August 12, small growth; August 20, good growth.

Ten days after starting sulfathiazole, following a chill and rise in temperature to 103°, an erythematous maculo-papular eruption appeared over the entire body and persisted. His temperature swung between 100° and 104°. Despite these toxic drug manifestations, sulfathiazole was continued three weeks longer. On its discontinuance the temperature immediately dropped to normal and the dermatitis quickly disappeared. For 19 days thereafter, he was afebrile, although a blood culture during this period (September 4) showed a heavy growth of *Streptococcus viridans*.

On August 28, sulfapyridine was begun and continued until December 8. The level of free sulfapyridine ranged between 4.5 and 5 mg. per cent. Repeated blood cultures were positive throughout.

There was no change in his febrile state. On several occasions he showed petechiae, and twice had symptoms of splenic infarction. Although blood cultures during September and October showed abundant growth, it was decided to administer heparin intravenously. His general condition at this time was good. Coagulation time, according to the method of Lee and White, was 3¼ minutes.

Heparin was begun on October 28 and continued uninterruptedly for 14 days. Because of the frequent reports of cerebral hemorrhages during the administration of heparin, it was decided not to prolong the clotting time to one hour, but to maintain it between 20 and 30 minutes. Coagulation time was determined every six hours, and exhibited moderate fluctuations. On a few occasions the coagulation time rose to 35 and 40 minutes, requiring alterations in the speed of heparin flow. A total of 660 c.c. of heparin was given. The average clotting time over the entire period was 23 minutes. There were no evidences of bleeding or infarction during this procedure.

There was no change in his clinical condition. Fever remained active. Blood culture, after one week of heparin, showed 45 colonies per c.c. of blood; after two weeks, 40 colonies per c.c. of blood. On November 25, two weeks later, he had a cerebral embolus. From this time on, his condition grew steadily worse, and he expired on December 26.

Autopsy was performed 30 minutes after death. The mitral valve showed a few granulations and rather easily detached, small, reddish, fungoid growths. The aortic valve was involved with massive amounts of similar granular, friable, reddish growths,

not only on the cusps but also in the aorta adjacent to the aortic valve and beneath the aortic valve on the surface of the left ventricle.

Microscopically, sections through the valve and vegetations showed large areas of necrosis and masses of densely packed, gram positive cocci.

To date, 55 cases treated with heparin and sulfapyridine have been reported.[7, 12, 13, 14, 15, 16, 17, 18, 19, 20]

Following their original series of seven cases, with "striking improvement" in three, Kelson and White treated 19 more, 18 of which were failures. Since the appearance of their paper others have appeared, reporting three recoveries and 26 failures.

An analysis of the seven cases benefiting from combined therapy discloses four that may be regarded as cured. One of these developed acute rheumatic fever and congestive failure, dying six months after treatment.[7] The heart at autopsy showed complete healing of the vegetations. The second case was well 18 months after treatment. However, the author states "an analysis of the therapy in this case suggests the probability that the success of the treatment would have occurred without the use of heparin. The febrile course was interrupted on the first day following commencement of sulfapyridine. The first negative blood culture was reported prior to the use of heparin."[16] The third case,[7] at the time reported, had been well 26 weeks after treatment, and the fourth had been well for six months.[17]

The fifth had "still remained free of evidence of the disease four weeks after stopping treatment."[7] However, conclusions cannot be drawn after such a brief interval since Capps states, "A considerable number of cases who become apparently well for months, or even a year or two, undergo a relapse with fresh bacteremia."[21]

In the sixth case, the diagnosis was not proved.[18] There are no published details available for the seventh case which has been reported as cured.[19] These cases of cure or improvement may well have been due to the sulfapyridine employed, since 12 from a total of 198 cases treated with sulfanilamide or sulfapyridine alone have been reported as cured.[19]

Of 22 heparin-treated cases where reported details are available, eight died of cerebral hemorrhages during the administration of heparin.

Discouraging as are the results of treatment by the sulfonamides, with apparently specific cures few and far between, they appear no more discouraging than those of the sulfapyridine-heparin combination. It would seem fair to conclude that heparin offers no advantages and has distinctly harmful potentialities. These facts, coupled with the expense and the difficulty of the control and management of the treatment, make very questionable the value of its further employment in the treatment of subacute bacterial endocarditis.

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UVEOPAROTITIS; A REPORT OF TWO CASES*

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DURING recent years there has been a decided increase in the number of reported cases of uveoparotitis. A rather comprehensive review of the literature reveals that approximately 100 such cases have been reported, less than 20 of which come from America and the remainder from foreign countries, chiefly Scandinavia, England and Germany. The rarity of this syndrome warrants the mention of additional cases and the careful scrutiny of these entities with regard to etiology.

* Received for publication May 28, 1940.

Parotitis, uveitis, and a low grade fever are the essential features of this condition. Prodromal symptoms, lasting for several weeks or months, include general malaise, drowsiness, weakness, nausea, vomiting, and loss of weight. Other signs and symptoms which are often encountered during the course of the illness include paralyses of the cranial nerve (particularly the seventh), a slightly elevated, discrete, erythematous rash occurring chiefly on the extensor surfaces of the forearms and legs, dryness of the mouth, various aching pains, polyuria and night sweats. Occasionally the submaxillary, sublingual or lacrimal glands are enlarged and also the cervical lymph glands.

The disease runs a chronic course, the symptoms lasting for months or for several years, and one of its features is the irregularity in the onset of symptoms. It may occur at any age, but is more common in the second and third decades and is slightly more prevalent in females. The morbidity is high whereas the mortality is low, only five deaths having been recorded.

The parotid glands are usually involved early in the course of the disease. They become enlarged and hard, and although not painful may be slightly tender. The glands are not adherent to the skin and never suppurate. The swelling, which is usually bilateral, lasts for months or years.

Inflammation in the uveal tract is present in all cases of uveoparotitis. The first ocular symptom is usually dimness of vision, associated with circumscribed corneal injection and narrowing of the palpebral fissures. Occasionally there is pain. Although in the beginning the involvement may be unilateral, bilateral uveitis usually follows. The pupils are often sluggish, dilated, or irregular, with a tendency to develop posterior synechiae. The other important eye findings which may be observed are fatty deposits on the posterior surface of the cornea, nodules in the iris, vitreous opacities, keratitis, optic neuritis and atrophy.

Reference is made to several excellent reviews of the literature on this subject, and no attempt will be made to duplicate such reports. The first description of this syndrome was given by Heerfordt [1] in 1909. Garland and Thompson,[2] Savin,[3] and Folger [4] have made comprehensive and critical surveys of the literature on this subject, while Levin [5] has reported in detail on the neurological aspect of the syndrome.

Case Reports

Case 1. A 35 year old negro male came to the Harbin Hospital on May 17, 1937, with a chief complaint of aching pain throughout the chest and abdomen associated with nausea and vomiting. On several occasions during the previous year he had had severe gastrointestinal "upsets" associated with aching pain in the chest and abdomen. His temperature had been moderately elevated for several days with these attacks. His employer stated that at times he was rather drowsy and acted as if he might be drugged, enough so that it was questionable whether he should continue his work as a chauffeur.

About three years prior to the time he was first seen he had consulted Dr. George B. Smith (ophthalmologist) because of dimness of vision, and in July 1934 a diagnosis of uveitis was made.

The patient's first wife had died of pulmonary tuberculosis in 1930, and one child by this wife was confined to a tuberculosis sanatorium at the time of his examination. His second wife was healthy. He used tobacco excessively and during each winter had frequent head colds with a slight cough. At the age of 20 he had had a gonorrheal infection, but no history of a chancre could be obtained.

Physical examination revealed a well developed, well nourished negro male not acutely sick. The lacrimal glands were swollen; considerable bilateral circumcorneal injection was present; the pupils reacted sluggishly to light and were irregular. Moderate dental caries and pyorrhea were present. Both parotid glands were enlarged, firm, smooth and slightly tender without any fixation of the skin. Upon being questioned, the patient stated that his wife had commented upon the appearance of each side of his face several times in the four or five months prior to the time of his examination. The submaxillary glands were not enlarged but several cervical lymph glands were palpable. Physical examination of the heart and lungs was not remarkable. The blood pressure was 120 mm. Hg systolic and 78 mm. diastolic. There was slight tenderness in the region of his umbilicus; otherwise his abdomen was negative. The biceps and patellar reflexes were normal. Dr. Smith reported that the uveitis had improved, that no posterior synechiae were present, and that his visual acuity was normal.

The first specimen of urine examined contained a small amount of albumin and a moderate amount of pus. Urinalyses at later dates, after the administration of urinary antiseptics, were negative. The blood findings were as follows: hemoglobin 92 per cent (Sahli), red blood cells 4,010,000, leukocytes 9,650, polymorphonuclears 60 per cent, eosinophiles 2 per cent, mononuclears 3 per cent, small lymphocytes 31 per cent, large lymphocytes 4 per cent. The blood Wassermann and blood Kahn reactions were negative. No malarial parasites were found. Examination of the spinal fluid revealed a cell count of 6, very small amounts of globulin and sugar, and a negative Kahn reaction. Colloidal gold showed no color change. A chest roentgenogram revealed normal lung fields and a cardiac outline within normal limits. The injection intradermally of 0.01 mg. of Old Tuberculin gave a positive reaction.

On June 15, 1937, the patient stated that he felt much better, that his drowsiness was less, and that no attacks of vomiting and abdominal pain had occurred. The physical findings on that date were unchanged. By request he returned on March 28, 1938 for a routine examination. Since last seen he had had two "slight attacks" of fever and general aching in the chest and abdomen, accompanied by vomiting. He stated that the enlargement of the parotid glands had varied in size, and they were found to be definitely smaller than at the time of his first examination. His sight had been good, and only a slight ciliary injection was noticed. He continued to be drowsy at times. The examination of his urine was negative.

He was seen again on June 24, 1938, at which time he had no complaint. The swelling of the lacrimal glands had disappeared and the eyes were grossly normal. The parotid glands continued to be slightly enlarged, chiefly on the right side. He had no nausea, vomiting, or aching pains, and his urine was negative. On March 2, 1940, he stated that his general health had been good since June of 1938. Very slight enlargement of both parotid glands was present, and the ophthalmologist reported normal eye findings.

This patient was not observed when he first had symptoms probably associated with uveoparotitis, as he reported dimness of vision almost three years before he was examined. As might be expected, in view of the intellect of the patient, the history regarding the duration of his general symptoms was vague. At no time did he take his condition seriously, and he was examined at the insistence of his employer.

Case 2. A 21 year old white American female came to the Harbin Hospital March 26, 1938 with a chief complaint of blurred vision in the right eye. For several days her right eye had been red, and the visual disturbance had been noticed for about two weeks. The patient stated that she had been a nervous person all her life but more so recently. At the age of 13 she was taken out of school for one year upon the advice of her physician because of a "rapid heart rate." Several years later she was told by another physician that she had a "leaking heart." It was not possible to elicit a history of any other cardiac disturbance. Two years prior to the time of her

examination she had had slight contact with a person who had active pulmonary tuberculosis. Otherwise her past history was not remarkable, and a review of her systems was non-contributory.

Physical examination revealed a poorly nourished, fairly well developed woman, 5 feet 4½ inches tall, weighing 108 pounds. Her temperature was 99.2° F. The pupils were equal, regular, and reacted to light and accommodation. A slight epicorneal injection was present in the right eye. The mouth was not remarkable, with the exception of slight dental caries. The parotid and submaxillary glands were not enlarged, neither were the cervical lymph glands. Examination of the heart and lungs did not reveal any positive findings, and the blood pressure was 118 mm. Hg systolic and 82 mm. diastolic. The abdomen was negative and the reflexes physiological. The blood count was as follows: hemoglobin 75 per cent (Sahli), red blood cells 3,760,000, leukocytes 7,500, polymorphonuclears 55 per cent, monocytes 2 per cent, eosinophiles 3 per cent, small lymphocytes 34 per cent, large lymphocytes 6 per cent. The urine was found to be normal, and the blood Kahn test was negative. A roentgenogram of her chest revealed normal lung fields and a cardiac outline within normal limits. A tuberculin test using 0.005 mg. of purified protein derivative tuberculin was negative.

During the following weeks her temperature ranged from normal to 100.5° F., and on April 22, 1938, a slightly elevated macular erythematous rash appeared on the arms, lower legs and feet. On April 29, 1938, an ophthalmological examination was made by Dr. F. P. Calhoun, and his report was as follows: "Vision right and left 15/15. The near points of accommodation were 10 cm.; there was no muscle imbalance and the intraocular tension was normal. The right eye showed a slight pericorneal injection, and the left eye showed a moderate pericorneal injection. Dilating the pupils for a fundus and slit lamp examination, many cells were found on the posterior surface of the right cornea; none was found on the left cornea although the aqueous beam was cloudy. With the ophthalmoscope vitreous cells were seen in the right eye but no other pathology, and the fundus of the left eye was normal. Diagnosis, bilateral cyclitis."

When the patient was seen on May 5, 1938, both submaxillary glands were enlarged and slightly tender. No enlargement of the parotid glands could be detected; the skin rash was still present and had not changed. After having been on a high caloric diet for several weeks she had gained about two pounds in weight. At that time she complained of a dry sensation in her mouth. On May 12, 1938 she stated that she had been nauseated for 18 hours and had vomited several times. During the few days preceding that date she had had various aching pains throughout her body which at times were severe. She continued to have a slight elevation in temperature, and her skin rash was fading. The ophthalmologist reported that her eyes were beginning to improve.

During the next few months she improved in general, the skin rash disappeared, her temperature was lower, and her eyes approached normal. The precipitates on the posterior surface of the cornea disappeared. On September 9, 1938, the left submaxillary salivary gland was not palpable, but the right continued to be slightly enlarged. By November 8, 1938, the patient was feeling very well and weighed 122 pounds. About one year later, in December of 1939, she complained that her vision was not quite normal, although it was fairly good. Dr. Calhoun reported as follows: "the vision was slightly improved and the slit lamp and fundus examinations were normal." Her general condition at that time was excellent.

During the early course of her illness therapeutic measures were instituted to improve her general condition. She was on a high caloric diet; ferrous sulphate was administered for the secondary anemia; she was in bed for several weeks; and efforts were made to relieve her nausea, aches and pains. At the suggestion of the ophthalmologist her pupils were dilated with atropine for several months until the cyclitis had completely subsided.

Comment

The first case presents typical findings of uveoparotitis. It is of interest to note that this patient had had much contact with active pulmonary tuberculosis and that his tuberculin test was positive. However, he did not have any clinical or roentgen-ray evidence of pulmonary tuberculosis. He improved considerably during the first few months he was under observation and after almost three years his condition continued to be good and his vision normal. The parotid glands were known to have been enlarged for about three years and were still enlarged at the time of his last examination in March 1940. No serological evidence of lues could be obtained.

In the second case the following characteristic findings of the uveoparotid syndrome are present: fever, bilateral cyclitis, skin rash, dryness of the mouth, nausea, vomiting, aching pains, and enlargement of the submaxillary glands. The fact that no enlargement of the parotid glands was detected makes a diagnosis of uveoparotitis questionable. In quite a number of the cases reported in the literature there was enlargement of the submaxillary or sublingual glands in addition to parotid enlargement. The authors feel that the evidence presented favors the diagnosis of uveoparotitis and would like to suggest that this syndrome may occur with enlargement of one of the salivary glands other than the parotids. Of interest is the fact that epidemic parotitis is known to occur with involvement of the submaxillary or sublingual glands, without any enlargement of the parotids.

The recognition of this condition is important from the point of view of prognosis and treatment. As a rule this disease is a self-limited one and treatment should be directed chiefly toward improvement of the patient's general condition, the alleviation of distressing symptoms, prevention of complications, and reassurance as to the probable outcome. One important therapeutic measure is the maintenance of mydriasis in an effort to avoid the formation of posterior synechia with permanent impairment of vision. Failing to diagnose this syndrome correctly may result in a faulty prognosis being given to its various manifestations, and may lead to unjustifiable treatment.

It has been established beyond any doubt that this syndrome is a well defined clinical entity. There is, however, a great diversity of opinion as to the etiology of this disease and a variety of causes have been suggested by authors who have reported cases. It is frequently referred to as uveoparotid tuberculosis, and in several cases evidence of tuberculosis has been obtained. There are those who believe that all such cases are tuberculous in origin but no sound proof has been offered to substantiate this theory. In the majority of cases tuberculosis has not been demonstrated, and the tuberculin reactions have been negative. Referring to this disease, Cohen and Rabinowitz [6] made the following statement: "the tuberculous patient is tuberculin sensitive except under conditions of massive tuberculous infection, but it must be conceded that the patients in this series had no massive infection, if at all infected, it was mildly, and yet the tuberculin reactions were negative in the majority of instances; in the cases in which the tubercle bacillus was demonstrated, the reaction was positive." It has been suggested by Lewis, Raines and Stewart [7] that this disease may not be due to any one specific infection but that it is a manifestation of local tissue hypersensitivity to any one of a variety of allergens, and that although tuberculin may

often be the allergen responsible, it is unwise to regard all cases of uveoparotitis as tuberculous. At the present time this appears to be the logical explanation of the cause of uveoparotitis. That it may be due to an organism which has not yet been identified must be considered. If the latter should be the case, this unknown organism apparently produces a low grade infection in a sensitized individual, the course of which is chronic with a spontaneous termination.

As it was not possible to demonstrate any primary tuberculous focus in the first case one cannot say that it was caused by tuberculosis, even though there was much contact with active pulmonary tuberculosis and the tuberculin test was positive. It must be remembered, however, that an infection of this type might have been present but not detected. In the second case the tuberculin reaction was negative, no causative agent was found, and its etiology remains unknown.

Summary and Conclusions

1. The findings in a typical case of uveoparotitis are described.

2. The possibility of this syndrome's occurring with involvement of one of the salivary glands other than the parotids is suggested and such a case is reported.

3. The importance of the recognition of this clinical entity is stressed.

4. The need of further knowledge of the etiology of uveoparotitis is pointed out. It is suggested that the syndrome may arise from hypersensitivity to a number of allergens.

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EDITORIAL

VACCINATION AGAINST RICKETTSIAL INFECTIONS

Two types of rickettsial infections are associated with so high a mortality and (at least, at some times) so high a morbidity that effective preventive measures are of great practical importance. These are epidemic ("Old World") typhus fever, and the Rocky Mountain spotted fever.

Spotted fever is conveyed to man by the bite of the wood tick. Man does not constitute an essential link in the life cycle of the infection. The natural reservoir of the virus is the tick, in which it passes from one generation to the next through the egg, and probably also various wild mammals on which the ticks feed. Man is only accidentally and incidentally infected.

The mortality of spotted fever varies greatly depending upon the virulence of the strain of virus involved and the locality in which it occurs. In Western Montana it may be 75 per cent or more, whereas in most regions, including the southeastern states, it is usually given as from 10 to 20 per cent. The incidence of the disease in the general population is so low that wide spread vaccination, if feasible, would hardly appear indicated. In those occupational groups, however, whose work exposes them to the bites of infected ticks, morbidity and mortality may both be high and any available means of protection most important. This applies, for example, to sheep herders, and to laboratory workers, particularly those handling infected ticks.

The theoretical possibility of securing protection by vaccination was indicated by the fact that recovery from natural infection was followed by a substantial degree of immunity. The U. S. Public Health Service, since the report of Spencer and Parker (1925), has employed a vaccine made by grinding up infected ticks in phenol-formalinized salt solution. Parker[1] has recently reported the results obtained over a period of 15 years. By giving two doses of 2 c.c. each, representing in all the virus obtained from five ticks, a substantial degree of protection was obtained. This was only temporary, however, and immunization had to be repeated annually. Reactions to the vaccine were usually mild, and no serious accidents were reported. Protection from the more virulent strains was only relative as a rule, but in the case of the milder types it was fairly complete. Thus during the period of 15 years, in an area of Western Montana in which the incidence of the disease was low but the mortality high, 51 cases of infection occurred in non-vaccinated individuals, with a mortality of 42, or 82 per cent; there were 37 cases in vaccinated adults, with a mortality of 3, or 8 per cent. Among their laboratory staff, 19 cases occurred in vaccinated individuals with one death, whereas 8 cases in unvaccinated individuals were all fatal. In a dis-

[1] PARKER, R. P.: Rocky Mountain spotted fever. Results of fifteen years prophylactic vaccination, Am. Jr. Trop. Med., 1941, xxi, 369–384.

trict in southern Idaho, in which the disease incidence was high but the mortality low, one case only occurred among 193 vaccinated, but there were 22 cases among 364 controls—a twelve fold difference. The course of the disease was milder and shorter in vaccinated cases.

Vaccines against tick-borne rickettsial strains in other localities (South Africa, South America) have been prepared in a similar manner, and have afforded protection in animal experiments. Thus far no extensive trials in man have been reported.

Typhus fever appears in two forms: the epidemic, or "old world" typhus, and endemic or murine typhus. These types are similar from the immunological standpoint, although they show quantitative differences, but they differ in their virulence, and in their epidemiology. Epidemic typhus is naturally a disease of man. Man constitutes the reservoir of the virus, and it is conveyed by the human body louse.

Endemic typhus is naturally a disease of rats which constitute the reservoir of the virus. It is conveyed like plague, by the rat flea (and from rat to rat also by the rat louse). It occurs sporadically in man, wherever man comes into close contact with these rodents and is exposed to the bites of infected fleas. It is widely distributed in seaports in the warmer climates, and is fairly common in the southeastern United States.

The virus of endemic typhus is more virulent for rodents, but in man causes a milder type of infection than does epidemic typhus, with a mortality in this country of less than 1 per cent, according to Dyer. Under such conditions, immunization on a large scale would hardly be worth the effort, although it might be desirable for those most intimately exposed.[2]

Epidemic typhus, on the other hand, once started, attacks large numbers of individuals and has a mortality rate varying from about 10 per cent to 70 per cent in different epidemics. In time of war, famine or other communal disasters, when epidemics of typhus are prone to occur, a general immunization of the population would manifestly be of the utmost value.

Recovery from typhus is followed by a substantial degree of resistance of considerable duration, although the occasional occurrence of second attacks indicates that it is not complete or permanent. Furthermore, for a short period after recovery protective substances can be detected in the serum. These facts indicate that theoretically at least, protection by vaccination should be possible.

The earlier attempts utilized living vaccines of murine typhus—of low virulence to man. Blanc attempted to attenuate the virus still further by suspending it in ox bile. Laigret made a suspension of infected guinea pig brain tissue in egg yolk, desiccated this, and later resuspended it in olive oil. Such vaccines were extensively used in the French colonies in northern Africa where it is reported over a million individuals were vaccinated. It is difficult to evaluate the results obtained. Laigret et al.[3] reported in detail

[2] Dyer, R. E.: The control of typhus fever, Am. Jr. Trop. Med., 1941, xxi, 163–184.

[3] Laigret, J., et al.: La vaccination contre le typhus exanthématique par la vaccine enrobé de l'institut Pasteur de Tunis, Arch. Inst. Pasteur de Tunis, 1937, xxvi, 454–623.

regarding a group of 32,481 vaccinated individuals in a population of 212,000. They reported five "certain" and eight "suspected" cases of murine typhus—all mild—developing as a direct result of the vaccination. However, vaccine was given extensively to groups in which an epidemic of typhus was developing and the disease appeared in an appreciable number of cases within a short time (less than two weeks) after vaccination. In all such groups, the epidemic subsided within three weeks. The incidence of typhus developing one month or more after vaccination was less than one per thousand, and all such cases recovered. The total number of cases in the entire population of 212,000 was 2,634, with 298 deaths. It appears, therefore, that the vaccine conferred a substantial degree of immunity for a period of at least one to two years. The use of a living vaccine, however, cannot be regarded as desirable, or under ordinary conditions as justifiable, in view of the risk involved, both to the individual inoculated, and to the community at large.

Many attempts have been made to use killed vaccine. Weigl first prepared an epidemic typhus vaccine by grinding up the intestines of infected lice in carbolized salt solution. The lice were infected by rectal injections of a suspension of rickettsiae; they were fed for a week on immune individuals, and the intestinal tract was then dissected out. By means of this vaccine, he apparently secured a substantial degree of protection in man. However, as it required about 100 lice to provide vaccine for a single individual, the procedure is obviously useless for immunization on a large scale.

Zinsser first secured the virus in abundance by intraperitoneal inoculation of endemic typhus into rats which had been poisoned with benzol or by radiation. The exudate was suspended in formalinized salt solution, and was shown to afford protection in animal experiments. Varela reported administering the vaccine to over 2,000 human cases without accident. No data were given as to the degree of protection obtained. Castaneda [4] obtained suspensions from the lungs of rats, in which a rickettsial pneumonia had been produced by intranasal inoculation. With this vaccine he obtained protection in guinea pigs and in a few human volunteers. Adequate amounts of murine vaccine protect animals from epidemic typhus as well as endemic typhus, although it gives quantitatively more effective protection from the latter type.

Attempts have also been made to utilize tissue culture suspensions as a source of vaccine. Zinsser [5] used minced 10 day chick embryos on serum agar. Cox [6] inoculated the yolk sac of developing chick embryos by direct injection of rickettsial suspensions. By both methods an abundant growth of rickettsiae can be obtained. Technically, Cox's method promises to be

[4] CASTANEDA, M. R.: Experimental pneumonia produced by typhus rickettsiae, Am. Jr. Path., 1939, xv, 467–475.

[5] ZINSSER, H., PLOTZ, H., and ENDERS, J. F.: Mass production of vaccine against typhus fever of the European type, Science, 1940, xci, 51–52.

[6] COX, H. R., and BELL, E. J.: Epidemic and endemic typhus: protective value for guinea pigs of vaccines prepared from infected tissues of the developing chick embryo, Pub. Health Rep., 1940, lv, 110–115.

the most satisfactory. By such culture methods it is possible to secure the virus of epidemic typhus in abundance, as well as murine typhus. This one would expect to be quantitatively more effective than the murine vaccine in man as a protection from the epidemic disease. With this vaccine Cox was able to protect guinea pigs, but so far no reports have appeared regarding its use in man.

Thus far none of these killed vaccines has been used in man, under epidemic conditions. The present war has created conditions in eastern Europe which seem ideal for the development of extensive epidemics of typhus. We may hope that this opportunity can be utilized to test the efficacy of these vaccines on a large scale. Thus far one may say only that the prospects are promising, but the procedure is still in the experimental stage. The value of the spotted fever vaccine for those who are exposed to the infection may be regarded as established, although there is still uncertainty as to the degree and duration of the protection.

P. W. C.

ERRATUM

On page 168, ANNALS OF INTERNAL MEDICINE, January, 1942, sixth line from foot should read

The roentgen-ray examination of the kidneys showed a large calculus almost filling

REVIEWS

Radiologic Physics. By CHARLES WEYL, S. REID WARREN, JR., and DALLETT B. O'NEILL. 459 pages, 24 × 16 cm. Charles C. Thomas, Springfield, Illinois. 1941. Price, $5.50.

This volume is divided into two parts: (1) the theory and practice of electrical engineering as applied to radiological apparatus; (2) the theory and application of radiation physics with reference to roentgen-ray diagnosis and roentgen- and gamma-ray therapy.

The authors have produced a clear and well integrated development of the fundamental theories underlying radiation technic starting with elementary electricity and mechanics and carrying the reader through an analysis of electric circuits, electrical instruments and apparatus, and electronics to a consideration of the theory of radiant energy, roentgen-rays and matter, and radioactivity and nuclear physics.

The technical and teaching experience of the authors is reflected in the excellent treatment of the practical aspects of radiation technics, the measurement and control of roentgen-rays and gamma-rays, and variations of exposure factors. The mathematics necessary to the formation of accurate concepts of the various phenomena is developed along with the theory. The simplicity of presentation and addition of a good appendix on the elements of algebra, trigonometry, and calculus permit a ready grasp of the subject by those without advanced training and are of particular value for the clinician who has been too long away from mathematical problems.

An exception to the thorough treatment of the different subjects prevalent in most of the book exists in the chapter on electromedical apparatus in which some sections, as for example those dealing with infra red and ultra violet radiation and electrocardiography, are so brief as to be hardly worth inclusion. In view of its possibilities for deep therapy more might be written of the van de Graff high voltage type of roentgen-ray generator. Also, it would be useful to have a more complete listing of the new artificially radioactive substances included in any future editions.

Of especial value to active workers in this field are the tables of useful data and the many helpful charts, graphs and diagrams given throughout the book. Each chapter is followed by an adequate and up-to-date list of special and general references. Last but not least is the section on safeguards against roentgen-ray burn and shock.

R. H. O.

Applied Pharmacology. By HUGH ALISTER MCGUIGAN, PH.D., M.D., F.A.C.P. 914 pages; 25 × 17 cm. The C. V. Mosby Co., St. Louis. 1940. Price, $9.00.

This text is a comprehensive treatise dealing with the application of pharmacological information to therapeutics. The approach to the subject matter is one representing pharmacodynamics as the scientific basis of the clinical use of drugs.

The book is divided into 86 sections. Drugs having related pharmacological action are classed together. A number of interesting and, for pharmacology texts, novel sections have been included. Thus, one finds chapters on barometric pressure, incidental conditions of the air, the reticulo-endothelial system, water, odors and the pharmacology of ganglia. The usual subdivisions of this subject are given in detail. Twenty pages are devoted to the principles of prescription writing. A well selected bibliography is appended to each section.

From the standpoint of the teacher of pharmacology the volume is to be recommended. Students will find the information clearly presented and well documented with tables, illustrations and structural formulas. The therapeutic approach also will appeal to most students.

The physician will find this volume a valuable reference work although the treatment of some of the newer drugs is extraordinarily brief. For example, only four pages have been devoted to the sulfonamide drugs. On the other hand some sections, for example, anesthesia, have been given in great detail. The discussion on theories of anesthesia is excellent.

The author is to be commended for his modern treatment of the section on prescription writing. He recommends the use of English instead of Latin and points out the therapeutic advantage of simple, one-drug medication.

The typography and composition of the book are of the usual creditable quality of the publisher.

C. J. C.

Headache and Head Pains. By WALTON FOREST DUTTON, M.D. 301 pages; 23.5 × 15.5 cm. F. A. Davis Co., Philadelphia. 1939. Price, $4.50.

The author lists in alphabetical order over 200 conditions associated with headache and head pain. He very briefly discusses their etiology, symptomatology, and treatment. The material is not arranged in a manner favorable for use as a differential diagnosis. A considerable portion of the text is devoted to prescriptions, which are in many instances sedatives and reappear with slight variations throughout the book. Under treatment the author also includes prescriptions directed toward the specific disease. Head pain per se is discussed only briefly in the introduction. He has not seen fit to become involved with the severe type of protracted headache of vague etiology which so frequently baffles the physician. The book is not recommended.

E. F. C.

The Principal Nervous Pathways. By ANDREW THEODORE RASMUSSEN, PH.D. 73 pages; 28.5 × 21.5 cm. The Macmillan Company, New York. 2nd edition, 1941. Price, $2.50.

This book was originally published in 1932 and has since been used for medical teaching. The general construction of the second edition is unchanged, consisting of the same number of schemas with accompanying explanations. Changes have been made in regard to the lateral spinothalamic tract, arrangement of the fibers in the thalami, position of the fibers in the medial lemniscus, and fiber connections between the vestibular nuclei and flocculonodular lobe of the cerebellum. Other minor changes have been made in the text to achieve a greater clarity of presentation. The author has made every effort to present the neural systems in a simplified manner, and has felt it necessary in some instances to fill in on the basis of logical assumption where actual knowledge is lacking. This in no way detracts from the usefulness of his charts.

E. F. C.

Hemorrhagic Diseases: Photo-Electric Study of Blood Coagulability. By KAARE K. NYGAARD, M.D. 320 pages; 24.5 × 16.5 cm. C. V. Mosby Co., St. Louis. 1941. Price, $5.50.

This monograph is concerned chiefly with the exposition of a new technic, devised by the author, based on the photo-electric principle for the study of blood coagulation. It is divided into three parts. Part I concerns itself with a historical review of methods for determining the coagulability of the blood. These methods have been conveniently divided into four groups, namely, those based on viscosimetry; optical methods; Van Allen's method; and plasma coagulability tests. The author's method falls into the second group. Succeeding chapters in Part I deal with fundamental principles of the photo-electric method. A description of the instrument devised by

the author, the photelgraph; and a discussion of photelgraph tracings known as coagelgrams. In brief, the technic consists in placing recalcified citrated plasma in the photelgraph which is designed to record automatically, in the form of a tracing, the succeeding changes in density of the fluid as it progresses from a liquid state to a gel. Time intervals are ruled on the specially prepared paper and various portions of the graph are marked by letters much in the manner of the electrocardiograph. The significance of various portions of the graph is considered. In Part II are included chapters discussing, with particular reference to the photelgraph technic, various experimental investigations on the coagulability of blood plasma. Part III deals with a study of various hemorrhagic diatheses by this procedure.

Important aspects of the problem of blood coagulation still urgently demand solution. New technics are always of value in advancing the horizons of knowledge. However, comparatively little new data concerning either of these fundamental problems or their abnormalities in the hemorrhagic blood dyscrasias have been added by this procedure. The volume represents a considerable amount of carefully done work. It can be recommended to all students of this question. Extensive bibliographies at the end of each chapter are an excellent feature of the book.

M. S. S.

COLLEGE NEWS NOTES

New Life Members of the College

The following Fellows of the American College of Physicians have subscribed to Life Membership, and their initiation fees and Life Membership subscriptions have been added to the permanent Endowment Fund of the College:

Dr. F. Gorham Brigham, Brookline, Mass.
Dr. William H. Bunn, Youngstown, Ohio
Dr. Curtis Crump, Asheville, N. C.
Dr. Samuel L. Gabby, Elgin, Ill.

Gifts to the College Library

The following gifts to the College Library of Publications by Members are gratefully acknowledged:

Books

Dr. Oscar G. Costa-Mandry, F.A.C.P., San Juan, P. R.—"Manual De Laboratorio de Salud Pública."

Reprints

Dr. Edward W. Anderson, F.A.C.P., Des Moines, Iowa—1 reprint;
Dr. Irving Greenfield (Associate), Brooklyn, N. Y.—2 reprints;
Dr. Augustus A. Hall, F.A.C.P., Columbus, Ohio—1 reprint;
Dr. Rudolph H. Kampmeier, F.A.C.P., Nashville, Tenn.—42 reprints;
Dr. Manfred Kraemer, F.A.C.P., Newark, N. J.—5 reprints;
Dr. William G. Leaman, Jr., F.A.C.P., Philadelphia, Pa.—1 reprint;
Dr. Robert C. Page (Associate), Mount Vernon, N. Y.—2 reprints;
William C. Pollock, F.A.C.P., Lieut. Col. (M. C.), U. S. Army—2 reprints;
Dr. Hugh P. Smith, F.A.C.P., Greenville, S. C.—1 reprint;
Dr. Samuel E. C. Turvey, F.A.C.P., Vancouver, B.C., Canada—1 reprint;
Dr. Edwin E. Ziegler, F.A.C.P., Boston, Mass.—2 reprints.

Nominations for A. C. P. Elective Offices

In accordance with the By-Laws of the American College of Physicians, Article I, Section 3, the following nominations for the elective offices, 1942–43, are herewith announced and published:

President-Elect ..... Ernest E. Irons, Chicago, Ill.
First Vice President ..... Charles H. Cocke, Asheville, N. C.
Second Vice President ..... Henry R. Carstens, Detroit, Mich.
Third Vice President ..... A. Comingo Griffith, Kansas City, Mo.

The election of nominees shall be by the members of the College at its Annual Business Meeting, St. Paul, Minn., April 23, 1942. These nominations do not preclude nominations made from the floor at the Annual Meeting itself. Nominations

for members of the Board of Regents and members of the Board of Governors will be presented at the Annual Business Meeting.

Respectfully submitted,
F. Gorham Brigham, Boston, Mass.,
T. Homer Coffen, Portland, Ore.,
J. Morrison Hutcheson, Richmond, Va.,
Warren Thompson, Omaha, Nebr.,
Edward L. Bortz, *Chairman*, Philadelphia, Pa.
Committee on Nominations

Schedule of Examinations by Certifying Boards

The following Boards have announced schedules of their examinations as follows:

American Board of Internal Medicine: William S. Middleton, M.D., Secretary 1301 University Ave. Madison, Wis.	Written Examinations: October 19, 1942; applications for admission must be filed before September 1, 1942. Oral Examinations: St. Paul, Minn., April, 1942, in advance of the meeting of the American College of Physicians; Philadelphia, Pa., June, 1942, in advance of the meeting of the American Medical Association in Atlantic City.
American Board of Pathology: F. W. Hartman, M.D., Secretary Henry Ford Hospital Detroit, Mich.	Written and Oral Examinations: Washington University, St. Louis, Mo., March 30–31, 1942.
American Board of Pediatrics: C. A. Aldrich, M.D., Secretary 707 Fullerton Ave. Chicago, Ill.	Oral Examinations: Chicago, Ill., November 2–3, 1942, in advance of the meeting of the American Academy of Pediatrics; applications for admission must be filed before July 3, 1942.
American Board of Psychiatry and Neurology: Walter Freeman, M.D., Secretary 1028 Connecticut Ave., N.W. Washington, D. C.	Written Examinations: Boston, Mass., probably May 15–16, 1942, in advance of the meeting of the American Psychiatric Association; New York, N. Y., December, 1942.
American Board of Radiology: B. R. Kirklin, M.D., Secretary Mayo Clinic Rochester, Minn.	Oral Examinations: Atlantic City, N. J., June 4–6, 1942; November, 1942 (date and place not yet selected).

For further details and application forms communicate with the respective secretaries.

Regional Meeting of Kentucky Members

Fellows and Associates of the American College of Physicians of Kentucky held their annual regional meeting at Louisville January 10, 1942. At two o'clock in the afternoon the following clinical program was given at the Louisville City Hospital. Dr. J. Richard Gott, Jr., F.A.C.P., was in charge of arrangements.

"Observations of a Case of Subacute Bacterial Endocarditis Treated by Artificially Induced Hypothermia"—Herbert L. Clay, M.D.

"A Preliminary Appraisal of the Five-Day Treatment of Syphilis"—Adolph B. Loveman, M.D. (Associate, A. C. P.), Fred Hathaway, M.D.

"Peritoneoscopy"—Joseph E. Hamilton, M.D.

"Gelatin as a Substitute for Blood Plasma"—Harold Gordon, M.D., F.A.C.P.

Clinico-Pathological Conference—A. J. Miller, M.D., F.A.C.P., Morris Flexner, M.D., F.A.C.P.

An evening social hour and dinner were held at the Pendennis Club. Dr. Chauncey W. Dowden, F.A.C.P., Governor for Kentucky, was Toastmaster.

Forty-six College members were in attendance, and the meeting was considered a thoroughly successful one, except for the disappointment of the inability of the President and President-Elect of the College to be present.

New England Regional Meeting, American College of Physicians

In the fall of 1941 the Governors of the six New England states decided to hold a regional meeting in New England every year if war conditions permit. The first of these took place in Providence on January 14, 1942. It was a one day affair beginning with clinics at the Rhode Island Hospital from 10 to 12.30, lunch at the hospital, an afternoon scientific session at the Rhode Island Medical Library from 2 to 5.30, and a shore dinner at the Squantum Club in the evening.

The morning clinics were well attended and proved interesting. They consisted of a number of short talks, demonstrations and reports of cases by members of the staff and a few clinicians from other local hospitals. This session was arranged and conducted by Dr. Charles F. Gormly, F.A.C.P., Physician-in-Chief of the Medical Department.

In the afternoon the following program was presented under the chairmanship of Dr. Alex. M. Burgess, F.A.C.P., Governor for Rhode Island:

"Eight Cases of Essential Pentosuria." Dr. R. O. Bowman and Dr. I. A. Beck, Providence.

"Application of Bone Marrow Biopsy to Certain Clinical Diagnostic Problems." Dr. R. J. Williams (Associate), Providence.

"Pernicious Anemia Complicated by a Malignant Polyp of the Stomach." Dr. J. W. Wentworth and Dr. C. T. Bingham, F.A.C.P., Hartford.

"Sulfanilamide in the Treatment of Scarlet Fever." Dr. K. K. Gregory (Associate), Providence.

"The Modern Management of Addison's Disease." Dr. Michael F. DeMaio, Providence.

"Experimental Liver Necrosis Produced by Tannic Acid (and its clinical correlation)." Dr. R. E. Kendall (Associate), Hartford.

"Sarcoid from X-ray Standpoint." Dr. R. T. Ogden (Associate), Hartford.

"The Circle of Willis and Its Aneurysms." Dr. C. A. McDonald, Providence, and Dr. Milton Korb, Boston.

A paper on encephalitis which was to be given by Dr. John Dingle of Boston was omitted as Dr. Dingle was detained in the south on government business, and Dr. De Maio's paper was substituted.

In the evening, following one of the famous Rhode Island shore dinners at the Squantum Club, Dr. Roger I. Lee, F.A.C.P., President of the College, and Mr. E. R. Loveland, Executive Secretary, spoke. An address by Dr. O. H. Perry Pepper, F.A.C.P., Philadelphia, had to be omitted as Dr. Pepper was detained in Washington. Dr. Henry Heyl, lately neuro-surgeon to the American Hospital in Britain, who was stationed at Birmingham during the period of the most severe raids, gave an interesting talk on "Recent Medical Experiences in England." President Henry M. Wriston of Brown University and The Very Rev. John J. Dillon, President of Providence College, were guests. Dr. Gormly was Toastmaster.

There were 95 physicians registered for the afternoon session, and 96 tickets for the dinner were issued. The meeting was sponsored by the Governors of the six New England states and arranged by the Governor for Rhode Ishland with the aid of the following committee: Charles F. Gormly, F.A.C.P., General Chairman, Elihu S. Wing, F.A.C.P., William S. Streker, F.A.C.P., and John F. Kenney, F.A.C.P.

It was decided that the meeting next year will, if conditions permit, be held in Hartford, Connecticut.

In early January the Finlay Institute of the Americas was formed in Havana, Cuba. The commission from the United States consisted of Dr. James E. Paullin, F.A.C.P., Atlanta, Ga., Dr. Edgar Mayer, F.A.C.P., New York City, Dr. Thomas Mackie, F.A.C.P., New York City, Dr. Milton Kahn, New York City, and Dr. Morris Fishbein, Chicago. On the Cuban commission were three members of the College, namely, Dr. Angel Vieta, F.A.C.P., Dr. Felix Hurtado Galtés, F.A.C.P., and Dr. Octavio Montoro Saladrigas, F.A.C.P., all of Havana. A plan was formulated for the participation of the Americas in the promotion of the scientific and cultural relationships of the medical groups in the two countries and in the Americas. Dr. Paullin was named Chairman of the Scientific Committee of the United States.

Under the direction of the Advisory Committee on Postgraduate Courses, of which Dr. Edward L. Bortz, F.A.C.P., Philadelphia, Pa., is Chairman, the American College of Physicians arranged a series of "Postgraduate Nights" at the United States Naval Hospital in Philadelphia, February 2–5. The following program was presented with Henry L. Dollard, F.A.C.P., Captain (M. C.), U. S. Navy, Commanding Officer of the Naval Hospital, presiding.

February 2, 1942

General Medicine

"Medical Emergencies"—George Morris Piersol, M.D., F.A.C.P., Vice Dean and Professor of Medicine, University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa.

"Prophylaxis and Treatment of Virus Diseases"—Hobart Reimann, M.D. (By Invitation), Magee Professor of Practice of Medicine and Clinical Medicine, Jefferson Medical College, Philadelphia, Pa.

"Fatigue"—Charles L. Brown, M.D., F.A.C.P., Professor of Medicine and Head of Department of Medicine, Temple University School of Medicine, Philadelphia, Pa.

"Borderline Metabolic Deficiencies"—G. Harlan Wells, M.D., F.A.C.P., Professor of Medicine, Hahnemann Medical College, Philadelphia, Pa.

February 3, 1942

CARDIOVASCULAR DISORDERS

"Effort Syndrome"—WILLIAM D. STROUD, M.D., F.A.C.P., Professor of Cardiology, University of Pennsylvania Graduate School of Medicine and School of Medicine, Philadelphia, Pa.

"Criteria of Organic Heart Disease in Recruits"—FRANCIS CLARK WOOD, M.D., F.A.C.P., Assistant Professor of Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pa.

"Some Forms of Cardiac Derangement During War Service"—THOMAS M. MCMILLAN, M.D., F.A.C.P., Assistant Professor of Clinical Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pa.

"Cardiovascular Problems in Aviation"—J. M. BACHULUS, M.D. (By Invitation), Lieutenant Commander (M. C.), U. S. N., Senior Medical Officer and Flight Surgeon, U. S. Naval Air Station, Lakehurst, N. J.

February 4, 1942

NEUROPSYCHIATRY

"Personality Deviations"—EDWARD A. STRECKER, M.D., F.A.C.P., Professor of Psychiatry and Chairman of Department of Psychiatry, University of Pennsylvania School of Medicine, Philadelphia, Pa.

"Early Signs of Psychoses"—EARL D. BOND, M.D. (By Invitation), Vice Dean for Neurology-Psychiatry, University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa.

"Traumatic Neuroses"—GEORGE WILSON, M.D. (By Invitation), Professor of Clinical Neurology, University of Pennsylvania School of Medicine, Philadelphia, Pa.

"Malingering"—BALDWIN L. KEYES, M.D., F.A.C.P., Clinical Professor of Psychiatry, Jefferson Medical College, Philadelphia, Pa.

February 5, 1942

CHEMOTHERAPY

"Pharmacology and Toxicology"—HARRISON F. FLIPPIN, M.D., F.A.C.P., Associate in Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pa.

"Surgical Infections"—JOHN S. LOCKWOOD, M.D. (By Invitation), Associate in Surgery, University of Pennsylvania School of Medicine, Philadelphia, Pa.

"Medical Infections"—JOHN A. KOLMER, M.D., F.A.C.P., Professor of Medicine, Temple University School of Medicine and School of Dentistry, Philadelphia, Pa.

"Urinary Tract Infections"—CHARLES UHLE, M.D. (By Invitation), Associate in Urology, University of Pennsylvania School of Medicine, Philadelphia, Pa.

At the completion of the above program, the following letter was received from the Commanding Officer of the Naval Hospital:

February 6, 1942

"DR. EDWARD L. BORTZ, *Chairman*
Advisory Committee on Postgraduate Courses
American College of Physicians
Philadelphia, Pa.

"*Dear Dr. Bortz:*

"The Series of four 'Postgraduate Nights,' just completed last night at the Naval Hospital, Philadelphia, was an unqualified success, and I hope the idea may be the seed of a country-wide movement in the direction of intensive graduate instruction to medical officers of the armed forces.

"In time of peace, the Bureau of Medicine and Surgery of the Navy Department constantly maintains a number of medical officers under instruction in various graduate schools of medicine. Under war conditions it is not practicable to spare officers for weeks or months. Furthermore, in time of war there is a rapid and great increase in the size of the Medical Corps, active and reserve. Therefore, it would appear that the matter of graduate and refresher instruction should be carried to the men in the field, exactly as was done in the 'Postgraduate Nights.'

"To you as the organizer and director of the course at the Naval Hospital, I extend my sincere thanks and congratulations.

"With kindest regards.

Very Sincerely,
(Signed) HENRY L. DOLLARD,
Captain, (MC), U. S. Navy,
Commanding U. S. Naval Hospital,
Philadelphia, Pa."

Harry G. Armstrong, F.A.C.P., Major (MC), U. S. Army, in charge of research at the School of Aviation Medicine, Randolph Field, Tex., has been named to receive the John Jeffries Award given by the Institute of the Aeronautical Sciences.

This Award, given annually "for outstanding contributions to the advancement of aeronautics through medical research," will be conferred on Major Armstrong in recognition of his pioneering studies on the physiological and psychological effects of flying at high altitude and in high speed maneuvers. He was one of the first to recognize and accurately to describe some specific medical results of flying, such as aero-neurosis, a kind of mental and physical fatigue experienced by flyers under certain conditions; aero-otitis, an effect of high altitude and acrobatic flying on the human middle ear; and aero-embolism, a reaction similar to the "bends" suffered by deep sea divers which affects pilots who climb to high altitudes too rapidly and without proper safeguards.

Major Armstrong is a member of the Aero Medical Association, the Association of Military Surgeons and the American Medical Association. He is a Fellow of the American College of Physicians and of the Institute of the Aeronautical Sciences. He was chosen to receive the John Jeffries Award for 1941 by a committee consisting of Dr. G. W. Lewis, Director of Research of the National Advisory Committee for Aeronautics; Gill Robb Wilson, President of the National Aeronautic Association; Edgar S. Gorrell, President of the Air Transport Association of America; John R. Poppen, F.A.C.P., Captain (MC), U. S. Navy, President of the Aero Medical Association; Frank W. Caldwell, President of the Institute of the Aeronautical Sciences; and Lester D. Gardner, President of the Aeronautical Archives of the Institute.

The American Association of Industrial Physicians and Surgeons, and the American Industrial Hygiene Association will hold their joint Annual Convention in Cin-

cinnati, April 13–17, 1942. The central purpose of the meeting will be to provide a five-day institute for the interchange and dissemination of information on new problems as well as for the consideration of up-to-date methods of dealing with those that are well known. Important medical and hygienic problems associated with the present huge task of American industry will be presented and discussed in clinics, lectures, symposia, and scientific exhibits.

"Laboratory Policies and Requirements in the Examination of Water" is the title of a paper in the Puerto Rico Health Bulletin for December, 1941, by Dr. O. Costa Mandry, F.A.C.P. Dr. Costa Mandry is Director of the Public Health Laboratories of the Puerto Rico Department of Health.

Among the speakers at the 4th Annual Congress on Industrial Health, sponsored by the Council on Industrial Health of the American Medical Association, January 12–14, 1942, were:

Dr. Andrew C. Ivy, F.A.C.P., Chicago, Ill.—"The Physiology of Work";

Dr. T. Lyle Hazlett, F.A.C.P., East Pittsburgh, Pa.—"Industrial Health—A Separate Discipline";

Dr. Walter L. Bierring, F.A.C.P., Des Moines, Iowa—"Postgraduate Education in Industrial Health";

Dr. George E. Wakerlin, F.A.C.P., Chicago, Ill.—"Pulmonary Capacity Tests in Health and Disease."

A report on "Vitamin Administration in Industry" was presented by representatives of the Council on Foods and Nutrition and the Council on Industrial Health of the American Medical Association. Dr. James S. McLester, F.A.C.P., Birmingham, Ala., and Dr. Russell M. Wilder, F.A.C.P., Rochester, Minn., were among the members of these Councils who prepared this report.

Dr. Walter Lindsay Niles, of New York, N. Y., was elected a Fellow of the American College of Physicians on December 14, 1941, but notification of his death suddenly on December 22, 1942, removes his name from the Roster before official announcement of elections could be published.

Dr. William Nimeh, F.A.C.P., Mexico City, Mexico, on a recent visit to the United States read a paper entitled, "Contribution of the Arabs to Medicine," at a meeting of the Staff of the Mayo Clinic.

Dr. Charles F. Gormly, F.A.C.P., Providence, was recently appointed a member of the Advisory Council to the State Department of Health, by the Governor of Rhode Island.

The Alumni Association of the College of Medical Evangelists held its 8th Annual Postgraduate Assembly at the White Memorial Hospital, Los Angeles, Calif., December 7, 1941. Among those who participated in the program were:

Dr. Thomas Addis, F.A.C.P., San Francisco, Calif.—"Diagnosis and Treatment of Nephritis in Group Practice";

Dr. Roy E. Thomas, F.A.C.P., Los Angeles, Calif.—"Atypical Pneumonia";

Dr. Hans Lisser, F.A.C.P., San Francisco, Calif.—"Indications for and Modes of Administering Testosterone Compounds in the Male";

Dr. Percival A. Gray, Jr., F.A.C.P., Santa Barbara, Calif.—"Office Management of the Diabetic Patient."

Dr. Philip F. Barbour, F.A.C.P., Louisville, Ky., spoke on "Active and Passive Immunization of Tetanus" and "Rehabilitation of Poliomyelitis Patients" at a recent meeting of the Georgia Pediatric Society.

Dr. James Alex. Miller, F.A.C.P., Professor of Clinical Medicine, Columbia University College of Physicians and Surgeons, delivered the Linsly R. Williams Memorial Lecture of the New York Academy of Medicine, November 13, 1941. The subject of Dr. Miller's address was "Tuberculosis: The Known and the Unknown."

Dr. Tom D. Spies, F.A.C.P., Associate Professor of Medicine, University of Cincinnati College of Medicine, Cincinnati, Ohio, was presented the Award of Distinction of the American Pharmaceutical Manufacturers' Association at its meeting in Washington, D. C., December 8, 1941. This award is made annually to an investigator who, in the opinion of the committee, has made a fundamental contribution to public health in the field of drug therapy. The award was given to Dr. Spies in recognition of his work on nicotinic acid.

Dr. Carleton B. Peirce, F.A.C.P., Montreal, Que., has been appointed Associate Professor of Radiology at McGill University Faculty of Medicine.

Dr. Elmer L. Sevringhaus, F.A.C.P., College Governor for Wisconsin, has been elected an honorary foreign member of the National Academy of Medicine of Buenos Aires.

The Thomas Drake Martinez Cardeza chair of clinical medicine and hematology has been established at Jefferson Medical College of Philadelphia. Dr. Harold W. Jones, F.A.C.P., has been named the first incumbent. Funds have been provided by Thomas Drake Martinez Cardeza to carry on the work of the Charlotte Drake Cardeza Foundation for the study and investigation of diseases of the blood and allied conditions.

Navy Needs Additional Medical Officers

The Surgeon General of the Navy announces the need for additional medical officers of the U. S. Naval Reserve who are qualified in Medical Department specialties, including that of Internal Medicine. Applicants for appointment in the Medical Corps of the U. S. Naval Reserve may obtain full and detailed information concerning such appointments by applying to the Commandant of the Naval District in which they reside. The maximum age limitation for appointments in the Medical Corps of the U. S. Naval Reserve is fifty years of age.

Fellows of the American College of Physicians, who are physically and in other respects qualified for appointments, may apply for appointments in the Volunteer, Special Service Class of the U. S. Naval Reserve in their specialty (Internal Medicine, or other specialties in Internal Medicine).

If the address of the Commandant of the Naval District is not known, it is suggested prospective applicants address a communication to the Bureau of Medicine

and Surgery, Navy Department, Washington, D. C., for information concerning appointments in the Medical Corps of the U. S. Naval Reserve.

Postgraduate Course in Tuberculosis Withdrawn

Postgraduate course No. 11, Tuberculosis, scheduled for the period April 13 to 18, 1942, at the University of Colorado School of Medicine and Hospitals, Denver, Dr. James J. Waring, F.A.C.P. as Director, was withdrawn February 6 due to conditions arising primarily out of the war. Some of the instructors were momentarily expecting to be called to active service, and, furthermore, the registration to that date had been inadequate. The director of the course and his associates deeply regret this necessary action. The College also expresses keen disappointment because this course would have been an exceedingly good one and had been especially organized for a group of tuberculosis physicians in the College membership.

OBITUARIES

DR. FREDERICK TAYLOR LORD

Dr. Frederick Taylor Lord, F.A.C.P., was born in Bangor, Maine, January 16, 1875. He died in Boston, November 4, 1941. His life was one of quiet and sustained devotion to his professional work, to his family, and to his friends. His point of view toward medicine was that of the teacher and of the scholar. Always he sought to learn something new. Always he sought to make what he had learned available to others. He leaves behind many pupils grateful for the wise instruction which he gave, for the example of meticulous thoroughness which he set, and for the kindly friendship with which he blessed all those who shared his work. He possessed those qualities which Lord Tweedsmuir once said were necessary to the successful working of democracy—humility, humanity and humour. The last of these was often manifested by a twinkle in his eye of almost elfish jollity.

From Harvard he received his A.B. in 1897, and his M.D. in 1900. He served as Medical House Officer at the Massachusetts General Hospital in 1900 and 1901, and he remained on the staff of that institution, in one capacity or another, until his death. From 1912 to 1935 he was Visiting Physician, and after 1935 a member of the Board of Consultation.

He joined the teaching force of the Harvard Medical School in 1905 as Instructor in Clinical Medicine, and throughout his life he participated actively in the work of the School, as well as in that of the hospital. In 1930 he was made Clinical Professor of Medicine, and in 1935, Clinical Professor of Medicine, Emeritus.

Although he served hospital and school largely without pay, and made his living in the private practice of medicine, as had the great clinical teachers of the past, the chief focus of his work was in these institutions. In addition to his constant interest in dispensary and bedside teaching, throughout his life he always had some piece of research in progress. Early in his

career he persuaded Dr. J. Homer Wright to give him a laboratory in the Allen Street House of the hospital. In this cubby-hole—it was little more —he was to be found whenever he had spare time, working like a beaver on some problem such as the role of actinomyces in dental caries. (Contribution to the etiology of actinomycosis. The Experimental production of actinomycosis in guinea pigs inoculated with the contents of carious teeth, Boston Med. and Surg. Jr., 1910, clxiii, 82.)

When in 1917 Dr. Edsall was able to secure decent space for clinical research, Dr. Lord was given a somewhat ampler laboratory in which, over a period of years, he conducted with the able collaboration of Dr. Robert N. Nye, a series of valuable studies on the biology of the pneumococcus.

Within the field of internal medicine, diseases of the chest were always Dr. Lord's special interest. In 1907 he was entrusted by Osler to write the chapter on Diseases of the Pleura in the seventh volume of the system on "Modern Medicine," and in two succeeding editions in 1913 and 1925 he contributed the chapter on Influenza. In 1915 was published his "Diseases of Bronchi, Lungs and Pleura," which ever since has remained an important text on these subjects.

He was early engaged in the fight against tuberculosis, serving for many years as President of the Channing Home, one of the first special hospitals for the care of patients with advanced tuberculosis, and in the public aspects he shared by serving on Advisory Committees of the State Department of Public Health and the Boston City Health Department, and through his leadership in various societies.

When anti-pneumococcic serum appeared on the scene in 1913, Dr. Lord took an active part in studying its action on patients and, with the aid of The Commonwealth Fund, in making it available for use by physicians throughout the state. When chemotherapy arrived he studied that with equal intensity. He collaborated closely with Dr. Roderick Heffron in these problems, and with him wrote several books on the subject.

In World War I Dr. Lord went to the Balkans as a member of the American Red Cross Commission to Serbia, for the relief and rehabilitation of the small remaining Serbian population.

In World War II he was doing his bit by compiling data on the qualifications of physicians in Massachusetts, and by making studies on the evaluation of rabbit and horse serum in the higher types of pneumococcus pneumonia.

In addition to the usual medical societies, Dr. Lord belonged to the Association of American Physicians; the Interurban Clinical Club, of which he was a charter member, and in 1928 President; the American Society for Clinical Investigation; the American Clinical and Climatological Association; the American Association for Thoracic Surgery, of which he was President in 1932; the National Tuberculosis Association, of which he was Vice-President in 1938–39; and the Massachusetts Tuberculosis League, of

which he was President in 1928. He had been a Fellow of the American College of Physicians since 1929.

Thus was his life full of good works, and long will the memory of this gentle, kindly, generous physician warm the hearts of those who knew him.

J. H. M.
F. M. R.

DR. CHARLES BRADFORD SYLVESTER

Dr. Charles Bradford Sylvester, F.A.C.P., of Portland, Maine, died December 18, 1941, as the result of heart and kidney disease.

Dr. Sylvester was born in Casco, Maine, February 12, 1865. He was graduated from Bridgton Academy in 1884 and five years later was granted a degree in medicine from the Bowdoin Medical School. He served as house physician at the New York Infants Hospital and Randalls Island Hospital in 1889 and 1890 and in the latter year he opened an office in the town of Harrison, Maine, where he practiced, with a single interruption, for 28 years. The interlude was provided by a graduate course in pathology at the Harvard Medical School in the years 1909 and 1910. Although his practice was perforce a general one, including obstetrics and minor surgery, the doctor's main interest was in medicine and he came to enjoy a considerable reputation as a medical consultant among the physicians in the region where he lived. He was President of the Oxford County Medical Society in 1908.

Early in 1918 Dr. Sylvester was given a commission in the Medical Reserve Corps of the U. S. Army. During the next two years he was on duty in the Tuberculosis Service at Camps Oglethorpe and Sevier and at General Hospitals No. 16 and No. 17. His interest in military medicine continued for the remainder of his life; he maintained his commission in the Medical Reserve Corps until he was retired because of age in 1929 with the rank of Lieutenant Colonel.

The duty assignment given Dr. Sylvester was entirely to his liking; it served to stimulate the interest which he already had in tuberculosis and this changed the course of his life. When he was discharged from service, in spite of the fact that he was nearly fifty-five years of age, he decided to settle in the City of Portland, Maine, and to confine his practice to internal medicine. The decision was a happy one. His fine personality, his ability and experience made him a popular consultant in diseases of the lungs. Within a short time he discovered a new interest in allergic respiratory diseases. As a member of a chest team, he visited and helped hold clinics in many of the cities and towns of the state. His energy and youthful enthusiasm seemed without limit. Our present system of tuberculosis survey of school children in Maine we owe in large part to the efforts of Dr. Sylvester. In recent years he conducted ragweed pollen surveys in Maine, the results of which were published in the New England Journal of Medicine.

Dr. Sylvester was Consulting Physician and Clinician in the Outpatient Department of the Maine General Hospital. He was a former President of the Cumberland County Medical Society, the Maine Medical Association, and the Maine Public Health Association. In 1939 he received the Maine Medical Association medal for fifty years of active medical practice. He was elected to Fellowship in the American College of Physicians in 1930. He was a Diplomate of the American Board of Internal Medicine, a Fellow of the American Medical Association, a Fellow of the American Academy of Tuberculosis Physicians, Director for Maine of the National Tuberculosis Association, a member of the Portland Medical Club, and President of the Board of Trustees of Bridgton Academy.

In spite of an active practice and his part in public health work, Dr. Sylvester found time to keep in touch with civic affairs, although he did not hold public office. He offered to his patients the sympathetic interest and understanding of the family physician; patients were never cases to him. His dealings with other practitioners were always above criticism. He loved youth, as he himself remained a youthful man, and younger doctors who knew him remember with gratitude his advice and help. In many respects Dr. Sylvester exemplified the finest attributes of the physician.

E. H. Drake, M.D., F.A.C.P.,
Governor for Maine.

DR. PETER A. REQUE

Dr. Peter Augustin Reque was born in 1869 at New Lisbon, Wisconsin, and died on December 4, 1941, in the Long Island College Hospital, Brooklyn, N. Y. He received his B.A. degree from Lutheran College, Decorah, Iowa; M.D. in 1896 from the University of Vermont College of Medicine; at one time he was on the faculty of the Long Island College Hospital and his practice was limited primarily to dermatology and urology.

Dr. Reque was a member of the Kings County Medical Society, Brooklyn Urological Society, South Brooklyn Medical Society, New York State Medical Society, the American Medical Association and he became a Fellow of the American College of Physicians in 1920. He served in France in the first World War with the rank of Major. He was a member of Cadaceus Post 818, a member of the American Legion, and was buried in Arlington National Cemetery.

Charles F. Tenney, M.D., F.A.C.P.,
Governor for Eastern New York.

PROGRAM
TWENTY-SIXTH ANNUAL SESSION
AMERICAN COLLEGE OF PHYSICIANS
ST. PAUL, MINN.

April 20–24, 1942

GENERAL SESSIONS AND LECTURES

Roger I. Lee, President

ST. PAUL COMMITTEE ON ARRANGEMENTS

John A. Lepak, General Chairman

James N. Dunn
Everett K. Geer
Charles N. Hensel
Gordon R. Kamman
Harold E. Richardson
Edward Schons

COMMITTEE ON CLINICS

Harold E. Richardson, Chairman
Alfred Hoff, Co-Chairman

Joseph F. Borg	Bethesda Hospital
Raymond H. Beech	Mounds Park Hospital
Lyman R. Critchfield	Ancker Hospital
Joseph N. Gehlen	Ancker Hospital
John Holt	Ancker Hospital
Lillian L. Nye	Ancker Hospital
Harry Ghent	St. John's Hospital
Frank G. Hedenstrom	Children's Hospital
Max Hoffman	Charles T. Miller Hospital
Joseph W. Jesion	Northern Pacific Hospital
Harry Oerting	St. Luke's Hospital
Joseph M. Ryan	St. Joseph's Hospital
Benjamin B. Souster	Midway Hospital
Cecil J. Watson	University Hospitals

COMMITTEE ON HOTELS AND TRANSPORTATION

Gordon R. Kamman, Chairman

Harvey O. Beek
Francis W. Lynch
John P. Medelman
Alfred J. Ouellette

COMMITTEE ON ENTERTAINMENT

James N. Dunn, Chairman
Edward V. Goltz, Vice Chairman

Edward C. Gibbs
John Meade
Arnold E. Naegeli

COMMITTEE ON AUDITORIUM

Edward Schons, Chairman
Frederick C. Schuldt, Vice Chairman

J. Richards Aurelius
Woodward Colby
William R. McCarthy
Burtis J. Mears
Fritz R. Pearson
Mark E. Ryan

COMMITTEE ON PUBLICITY

Charles N. Hensel, Chairman
Robert M. Burns, Vice Chairman

Harold H. Fesler
Emmet V. Kenefick
Alex E. Venables
Benjamin A. Weis

COMMITTEE ON PANEL DISCUSSIONS

Everett K. Geer, Chairman
Edward C. Gager, Vice Chairman

John F. Briggs
Edgar T. Herrmann
Alexander R. Hall
Kano Ikeda
George N. Ruhberg
J. Allen Wilson

COMMITTEE ON LADIES' ENTERTAINMENT

Mrs. Edward V. Goltz, Chairman

Mrs. J. Richards Aurelius
Mrs. John F. Briggs
Mrs. James N. Dunn
Mrs. Edward C. Gager
Mrs. Everett K. Geer
Mrs. Alexander R. Hall
Mrs. Edgar T. Herrmann
Mrs. Alfred Hoff
Mrs. Kano Ikeda
Mrs. Gordon R. Kamman
Mrs. John A. Lepak
Mrs. Harold E. Richardson
Mrs. Edward Schons
Mrs. Benjamin B. Souster

HONORARY COMMITTEE

Living Past Presidents

James D. Bruce
O. H. Perry Pepper
William J. Kerr
James H. Means
Ernest B. Bradley
James Alex. Miller
Jonathan C. Meakins
George Morris Piersol
Francis M. Pottenger
S. Marx White
Sydney R. Miller
John H. Musser
Charles F. Martin

A WELCOME TO THE AMERICAN COLLEGE OF PHYSICIANS

With hand outstretched in ever welcome greeting to you all,
We take you to our own and wish you well, hoping the while
That you may find the hospitality of old Saint Paul
Something to remember of our frank mid-western style.

To this illustrious group, may we say that we are glad indeed
To have you with us now, adding a luster e'en anew
To an ever glowing past, which, springing from a tiny seed,
Now stands a flowering city, where once a forest grew.

Proud are we of our heritage, fruits of efforts made by men,
Hardy pioneers, empire builders, saints and scholars all,
Who blazed our trails and laid foundations well, that we who follow them
May bravely bear the torch and write new ere life's shadows fall.

See our city from the heights of Cherokee at night,
Where years ago embattled Indians fought, and looking North,
See myriads of vari-colored twinkling lights
Reflected on the river now peacefully flowing forth:

Still farther North, in silhouette against emblazoned sky,
Our State House stands, a symbol of the freedom in our land,
And to the left, atop a hill, green domed with arms stretched high,
Saint Paul's Cathedral testifies the love of God for man:

Far to the right above the river's bend, the Indian Mounds
Where dead Sioux Chieftains lie, facing the east against the rising sun,
Waiting the dawn of life anew in the happy hunting grounds
Waiting with the Mounds and the river 'til the sands of time are run.

This is our city of bluffs and bridges under whose broad spans
The mighty Mississippi flows silently to the sea
Upon whose calm expanse is mirrored on history's page
Journeys of ancient voyageurs for all posterity.

These are the things we love, this is our home and for the time
'Tis yours who gather with us here in common brotherhood,
Who foster now the theme of "man's humanity to man"
That in these trying times it seems is little understood.

To this grand assemblage gathered, let us rise and give a toast,
From dawn of day to setting sun, from North, South, East and West,
Reverberating from our seven hills, Saint Paul the gracious host,
May ring in pleasant memory forever as the best.

J. J. R.

GENERAL INFORMATION

St. Paul Headquarters

General Headquarters—Municipal Auditorium

Hotel Headquarters—Hotel Lowry and Hotel St. Paul, jointly

The St. Paul Municipal Auditorium will be General Headquarters for registration, exhibits, general sessions, panel discussions and special lectures.

The Hotel Lowry will be headquarters for Officers, Regents, Governors and Committeemen. However, Hotel St. Paul, located near-by, will serve as joint headquarters for members of the College.

List of St. Paul Hotels	Blocks from Municipal Auditorium	Rates per day, with private bath	
		Single Room	Double Room
HOTEL LOWRY	3½	$2.50–5.00	$4.00–7.00
HOTEL ST. PAUL	2	2.50–5.00	3.50–7.00
Angus	10	2.00–2.50	3.00–3.50
Capitol Apts.	4	2.50	4.00
Commodore	10	2.50–5.00	3.50–6.00
Frederic	5	1.75–2.50	2.50–4.00
Grand	2	1.75–2.00	2.50–3.00
Jewell	4½	2.00	2.50
Ryan	8	2.00–3.00	3.00–5.00
St. Francis	3	2.50–3.50	3.50–4.50

Members should make reservations directly with hotels of their choice. Mention the Convention of the American College of Physicians, for rates quoted are, in some instances, only for this occasion.

WHO MAY REGISTER—

(*a*) All members of the American College of Physicians in good standing for 1942 (dues, if not paid previously, may be paid at the Registration Bureau).

(*b*) All newly elected members.

(*c*) Medical students pursuing courses at the University of Minnesota Medical School or The Mayo Foundation, upon presentation of matriculation cards, or other evidence of registration at these institutions; exhibits, morning lectures, general sessions.

(*d*) Members of the staff, including interns, of the hospitals participating in the program, without registration fee, upon presentation of proper identification; exhibits, morning lectures, panel discussions and general sessions.

(*e*) Members of the Ramsey and Hennepin County Medical Societies, without registration fee, upon presentation of membership cards in their respective societies.

(*f*) Members of the Medical Corps of the Public Services of the United States and Canada, without registration fee, upon presentation of proper credentials.

(*g*) Qualified physicians who may wish to attend this Session as visitors; such physicians shall pay a registration fee of $12.00, and shall be entitled to one year's subscription to the ANNALS OF INTERNAL MEDICINE (in which the proceedings will be published), included within such fee.

REGISTRATION BUREAU—Temporary Registration Bureau will be open at the Municipal Auditorium on Sunday, April 19, from 2:30 to 5:00 in the afternoon and from 7:00 to 9:00 in the evening. The permanent Registration Bureau at the Auditorium will be open daily 8:30 a.m. to 6:00 p.m., Monday to Friday, April 20–24.

REGISTRATION BLANKS FOR ALL CLINICS AND PANEL DISCUSSIONS will be sent to members of the College with the formal program. Guests will secure registration blanks at the Registration Bureau during the Session.

BULLETIN BOARDS FOR SPECIAL ANNOUNCEMENTS will be located near the Registration Bureau at the Municipal Auditorium and in the lobby of the headquarters hotels.

TRANSPORTATION—There will be no special convention rates in connection with national transportation. However, in many instances, reduced round trip tickets are in effect from certain localities. Consult your local ticket agent.

Local transportation arrangements are in charge of the Committee on Transportation, which will issue full information at the meeting.

THE GENERAL BUSINESS MEETING OF THE COLLEGE will be held at 4:40 p.m., Thursday, April 23, immediately following the general scientific program of the afternoon. All Masters and Fellows of the College are urged to be present.

There will be the election of Officers, Regents and Governors and the annual reports of the Secretary-General, Executive Secretary and Treasurer will be presented. The President-Elect, Dr. James E. Paullin, Atlanta, Ga., will be inducted into office.

BOARD AND COMMITTEE MEETINGS—The following meetings are scheduled as indicated. Special meetings will be announced and posted.

A *dinner meeting* of the Board of Regents and of the Board of Governors will be held at the Hotel Lowry, Spanish Room, mezzanine floor, Sunday evening, April 19, at seven o'clock.

COMMITTEE ON CREDENTIALS

Sunday, April 19, 9:00 a.m. . . . . Municipal Auditorium, mezzanine floor, Executive Secretary's Office.

BOARD OF REGENTS

Municipal Auditorium, mezzanine floor

Sunday, April 19, 2:30 p.m.
Tuesday, April 21, 12:00 m.*
Friday, April 24, 12:00 m.*

BOARD OF GOVERNORS

Municipal Auditorium, mezzanine floor

Monday, April 20, 5:00 p.m.
Wednesday, April 22, 12:00 m.*

SPECIAL FEATURES

Monday, April 20, 1942

THE ANNUAL SMOKER—Directly following the last presentation of the Second General Session on Monday evening, the so-called Annual Smoker of the College will be held in Stem Hall, which adjoins the theater in the Municipal Auditorium. There will be plenty of beer, tobacco, cold foods and refreshments, but, it is hoped, these will play only a secondary rôle to the renewed friendships, orchestral music, quartet singing, movies in technicolor of Big Game Hunting in Alaska and the St. Paul Winter Carnival, and general fun and merry-making.

The Entertainment Committee firmly believes that the above special Monday evening features will not only further the social aspects of the College but also enhance the purpose of the Annual Smokers.

Fellows and Associates, local and visiting physicians and the technical exhibitors are invited to attend the Smoker as guests of the College. The registration badge is all that is needed for identification.

Tuesday, April 21, 1942

ENTERTAINMENT BY THE RAMSEY COUNTY MEDICAL SOCIETY—8:00 p.m., Theater, Municipal Auditorium. In view of there being no scientific

* Buffet luncheon served.

program scheduled for Tuesday evening, the Ramsey County Medical Society will act as host to the College and present a program of entertainment, details of which will be revealed at the Session.

Wednesday, April 22, 1942

CONVOCATION OF THE COLLEGE—8:30 p.m., Theater, Municipal Auditorium. All members of the College and those to be received into Fellowship should be present. Officers, Regents, Governors and newly elected Fellows who have not yet been received in Fellowship are requested to assemble in the hall immediately above the theater lobby of the Municipal Auditorium at 7:45 o'clock, preparatory to the formation of the procession. They will be conducted to their seats by the Marshal of the Convocation promptly at 8:30. It is suggested that all appear in evening clothes.

The Convocation is open to all physicians and their families generally. A cordial invitation is also issued to such of the general public as may be interested.

The Convocation Ceremony will include the President's Address and the Convocational Address, which this year will be delivered by William deB. MacNider, Kenan Research Professor of Pharmacology at the University of North Carolina School of Medicine, Chapel Hill, whose title will be "A Consideration of the Factor of Change in the Animal Organism." The award of the John Phillips Memorial Medal for 1942 will be made to Dr. John R. Paul and Dr. James D. Trask, jointly, of New Haven, Conn. The recipients of the Research Fellowships of the College for 1942 will be announced. The newly elected Fellows will be presented by the Secretary-General, Dr. George Morris Piersol, and after subscribing to the Fellowship Pledge will be inducted by the President. The President's Reception and Dance will follow immediately after the Convocation in the Ballroom (mezzanine floor) of the Lowry Hotel. All members and their guests are requested to pass along the receiving line. Newly inducted Fellows should sign the Roster and secure their Fellowship Certificates during the Reception.

Thursday, April 23, 1942

THE ANNUAL BANQUET of the College will be held in the Ballroom of the Hotel Lowry at eight o'clock. Dr. John A. Lepak, General Chairman of the Session, will be Toastmaster. The address of the evening, entitled "Medicine and the Public," will be delivered by Dr. William A. O'Brien, Director of Postgraduate Medical Education, University of Minnesota.

All members of the College, physicians of St. Paul and Minneapolis, visitors attending the Session, guests and friends, with their families, are cordially invited. Table reservations for groups may be arranged. Orchestral music will enrich this occasion. For the benefit of those who are reluctant to attend banquets, because of too much speech-making, let it be known that the Banquet of the American College of Physicians is always a delightful exception. Tickets should be purchased at the Registration Bureau by Wednesday afternoon—price, $4.00.

PROGRAM OF ENTERTAINMENT FOR VISITING WOMEN

The wives of the St. Paul members of the College cordially invite all the visiting women at the College meeting in St. Paul to participate in the special program of entertainment arranged for them.

The visiting women are asked to register immediately upon arrival in St. Paul at their headquarters on the mezzanine floor, Hotel Lowry. There they will receive a program of entertainment and information about theaters, stores, restaurants and places of interest in and around St. Paul.

It is necessary to make reservations for some of the events on the Ladies' Program.

MONDAY, APRIL 20, 1942

Morning: Registration, mezzanine floor, Hotel Lowry.

Afternoon: 4:00 to 6:00 p.m. Tea of Welcome at the University Club as guests of the members of the Entertainment Committee and the Ramsey County Medical Auxiliary.

3:30 p.m. Buses leave Hotel Lowry for the University Club. Return at 5:30 p.m. to Hotel Lowry. Bus fare, $.50.

Evening: 9:30 p.m. Annual Smoker, Stem Hall, Municipal Auditorium. (Music, singing, technicolor movies, refreshments.)

TUESDAY, APRIL 21, 1942

Morning: Free.

Afternoon: 12:30 p.m. Luncheon and Style Revue by Schunemans, Albrecht Furs, and Helens, Inc. Luncheon in Terrace Cafe, Hotel Lowry. Tickets, $1.00.

Evening: 8:00 p.m. Entertainment by the Ramsey County Medical Society in the Theater, Municipal Auditorium.

WEDNESDAY, APRIL 22, 1942

Morning: 11:00 a.m. Tour of Radiation Therapy Department at the University of Minnesota and Coffman Memorial Union.

Afternoon: 1:00 p.m. Luncheon at Coffman Memorial Union. Tickets for luncheon, $1.00. Bus fare, round trip, $.50. Buses leave Hotel Lowry at 10:30 a.m. and return to hotel at 2:00 p.m.

Evening: 8:30 p.m. Convocation in the Auditorium Theater, followed by the President's Reception and Dance in the Ballroom, Hotel Lowry.

THURSDAY, APRIL 23, 1942

Morning: 11:00 a.m. Breakfast for members and guests, Terrace Cafe, Hotel Lowry.

Afternoon: 1:30 p.m. Buses leave Hotel Lowry for a tour of the city to visit some of the many interesting places, such as the Indian Mounds Park, Phalen Park, Como Park Conservatory, State Capitol, Minnesota Historical Building, St. Paul Art Gallery and School of Arts, Fort Snelling, Sibley House and the St. Paul City Hall and Court House. Bus fare, $.50.

Evening: 8:00 p.m. Annual Banquet of the College in the Ballroom, Hotel Lowry.

THE EXPOSITION AND TECHNICAL EXHIBIT will be located on the Arena Floor of the Municipal Auditorium. From the accompanying diagram, it will be noted that the Exhibit has a highly favorable location and arrangement. Members are urged to familiarize themselves with the Exhibit layout and to make it a point to visit all the exhibitors.

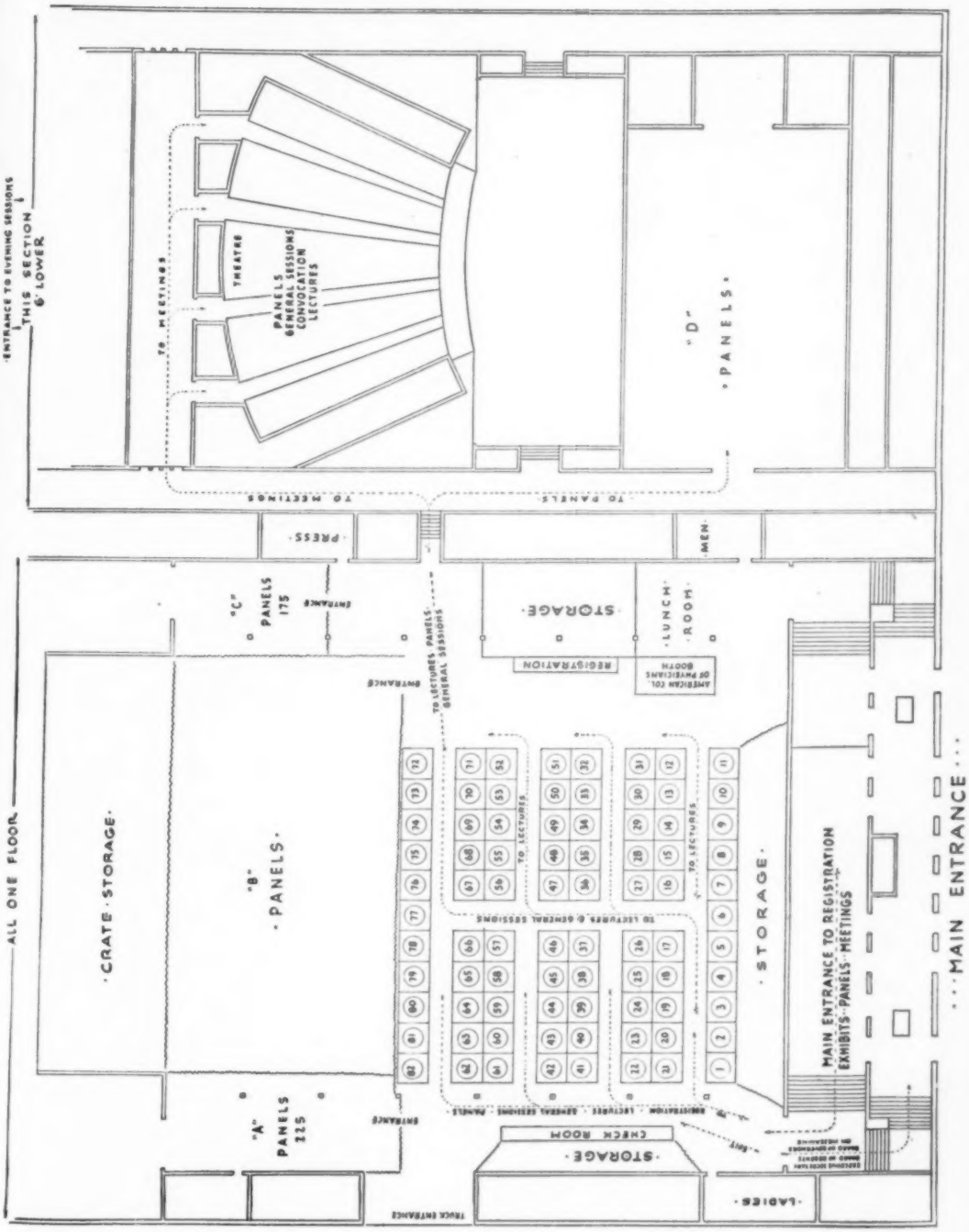
The American College of Physicians has put forward an organized effort to raise the standards of Technical Exhibits. All irrelevant products have been eliminated and only firms are invited who present a group of approved products of scientific interest to Internal Medicine and its allied specialties. Members of the College will readily distinguish the difference between this Exhibit and the general medical exhibit elsewhere, where frequently all sorts of products irrelevant to the actual practice of medicine are displayed and where methods of high pressure selling are common. The Exhibits sponsored by our College warrant the respect and interest of every physician. Here conveniently available will be the leading medical books, pharmaceuticals, apparatus and appliances, and many other products or services, making up much of the armamentarium of medical practice. These exhibitors and their displays merit your special attention, not only because of their educational value, but because of their contributions to the support of the Annual Sessions of the College.

Special intermissions in the general program have been arranged, providing additional time for the inspection of exhibits.

LIST OF EXHIBITORS

	Booth No.
Ayerst, McKenna & Harrison (U. S.) Ltd., Montreal, Que.	1
E. R. Squibb & Sons, New York, N. Y.	2–3
Smith, Kline & French Laboratories, Philadelphia, Pa.	4–5
D. Appleton-Century Co., Inc., New York, N. Y.	6
The Wm. S. Merrell Company, Cincinnati, Ohio	7–8
Winthrop Chemical Company, Inc., New York, N. Y.	9–10
Warren E. Collins, Inc., Boston, Mass.	11
J. B. Lippincott Company, Philadelphia, Pa.	12
Frederick Stearns & Company, Detroit, Mich.	13
Devereux Schools, Devon, Pa.	14
Lederle Laboratories, Inc., New York, N. Y.	15
The Williams & Wilkins Company, Baltimore, Md.	16
The Maltine Company, New York, N. Y.	17
The Cream of Wheat Corporation, Minneapolis, Minn.	18
Davies, Rose & Company, Limited, Boston, Mass.	19
The Medical Bureau, Chicago, Ill.	20
Paul B. Hoeber, Inc., New York, N. Y.	21
Oxford University Press, New York, N. Y.	22
White Laboratories, Inc., Newark, N. J.	26
The Armour Laboratories, Chicago, Ill.	27
Abbott Laboratories, North Chicago, Ill.	28
F. A. Davis Company, Philadelphia, Pa.	29
Schering Corporation, Bloomfield, N. J.	30
John Wyeth & Brother, Inc., Philadelphia, Pa.	31
Lea & Febiger, Philadelphia, Pa.	32
General Electric X-Ray Corporation, Chicago, Ill.	33–34
American Hospital Supply Corporation, Chicago, Ill.	35
William R. Warner & Company, Inc., New York, N. Y.	36
Sharp & Dohme, Philadelphia, Pa.	37–38–39–40
The Arlington Chemical Company, Yonkers, N. Y.	41
Jones Metabolism Equipment Co., Chicago, Ill.	42
Sandoz Chemical Works, Inc., New York, N. Y.	44
Hoffmann—La Roche, Inc., Nutley, N. J.	45
Bilhuber-Knoll Corp., Orange, N. J.	46
Eli Lilly & Company, Indianapolis, Ind.	47–48–49
Cameron Heartometer Co., Chicago, Ill.	50
Year Book Publishers, Inc., Chicago, Ill.	51
W. B. Saunders Company, Philadelphia, Pa.	52
Ciba Pharmaceutical Products, Inc., Summit, N. J.	53
Thos. Leeming & Co., New York, N. Y.	54
Merck & Co. Inc., Rahway, N. J.	55–56
The C. V. Mosby Company, St. Louis, Mo.	57
Hamilton Manufacturing Company, Two Rivers, Wis.	58–59
Cambridge Instrument Co., Inc., New York, N. Y.	61
Gerber Products Company, Fremont, Mich.	62
Cameron Surgical Specialty Company, Chicago, Ill.	67
Becton, Dickinson & Company, Rutherford, N. J.	69–70
Sanborn Company, Cambridge, Mass.	71

FLOOR PLAN OF THE TECHNICAL EXHIBIT AND MEETING ROOMS, MUNICIPAL AUDITORIUM



FLOOR PLAN OF THE TECHNICAL EXHIBIT AND MEETING ROOMS, MUNICIPAL AUDITORIUM

OUTLINE OF THE ST. PAUL SESSION

Auditorium events are indicated in **bold type**

TIME	MONDAY	TUESDAY		WEDNESDAY		THURSDAY		FRIDAY	
	April 20	April 21		April 22		April 23		April 24	
9:00 a.m. to 11:30 a.m.	Morning free **Registration, Exhibits, etc.**	Hospital Clinics	**Morning Lectures (9:30–11:30)**	Hospital Clinics	**Morning Lectures (9:30–11:30)**	Hospital Clinics	**Morning Lectures (9:30–11:30)**	Hospital Clinics	**Morning Lectures (9:30–11:30)**
12:00 m. to 1:15 p.m.		**Panel Discussions**		**Panel Discussions**		**Panel Discussions**		**Panel Discussions**	
1:15 p.m. to 2:15 p.m.	Luncheon	Luncheon		Luncheon		Luncheon		Luncheon	
2:15 p.m. to 5:00 p.m.	**1st General Session**	**3d General Session**		**4th General Session**		**5th General Session** **Annual Business Meeting**		**6th General Session**	
5:00 p.m. to 8:00 p.m.	Dinner	Dinner		Dinner		ANNUAL BANQUET			
8:00 p.m. to 11:00 p.m.	**2d General Session** followed by SMOKER			**CONVOCATION,** followed by President's Reception					

	Booth No.
Riedel—de Haen, Inc., New York, N. Y.	72
The Borden Company, New York, N. Y.	73
Mead Johnson & Company, Evansville, Ind.	74
Burroughs Wellcome & Co. (U. S. A.) Inc., New York, N. Y.	75
The Mennen Company, Newark, N. J.	76
H. J. Heinz Company, Pittsburgh, Pa.	77
Parke, Davis & Company, Detroit, Mich.	82

(As this program goes to press, the following spaces are unassigned: 23, 24, 25, 43, 60, 63, 64, 65, 66, 68, 78, 79, 80 and 81.)

GENERAL SESSIONS

"Medical Horizons" is the general theme of this program. The program of the General Sessions complements that of the clinics, panels and lectures. Certain timely topics are taken from the great wealth of medical advances. This program includes, among others, a discussion of aviation medicine and a discussion of the problems of old age. In some instances, the program represents continued reports on communications made at previous meetings of the College. At the New Orleans meeting of the College, Professor E. O. Lawrence, in the Convocation Address, discussed the cyclotron; in this program, we have a report of some of the clinical applications of that address.

GENERAL SESSIONS PROGRAM

Theater, Municipal Auditorium

FIRST GENERAL SESSION

Monday Afternoon, April 20, 1942

General Chairman, John A. Lepak, presiding

p.m.

2:15 Addresses of Welcome:

JOHN A. LEPAK, F.A.C.P., General Chairman, Twenty-sixth Annual Session, St. Paul, Minn.

CARL B. DRAKE, President of the Ramsey County Medical Society.

HERBERT Z. GIFFIN, F.A.C.P., President of the Minnesota Medical Association.

HAROLD S. DIEHL, Dean, University of Minnesota Medical School.

The Honorable JOHN J. MCDONOUGH, Mayor of St. Paul.

The Honorable HAROLD E. STASSEN, Governor of Minnesota.

Response to Addresses of Welcome:

ROGER I. LEE, F.A.C.P., President of the American College of Physicians.

3:30 INTERMISSION.

President Roger I. Lee, F.A.C.P., presiding

AVIATION MEDICINE

4:00 A Brief History of Aviation Medicine and the Physical Qualifications for Flying.

LOUIS H. BAUER, F.A.C.P., Consultant in Aviation Medicine and in Cardiology, Civil Aeronautics Administration, Hempstead, N. Y.

4:20 The Effects of High Speed Including Dive Bombing. Aero Embolism.
CAPTAIN JOHN R. POPPEN, (MC), U. S. Navy, F.A.C.P., Bureau of Aeronautics, Navy Department, Washington, D. C.
4:40 Oxygen Want and the Use of Supplementary Oxygen.
MAJOR HARRY G. ARMSTRONG, (MC), U. S. Army, F.A.C.P., Director of Research, School of Aviation Medicine, Randolph Field, Tex.
5:00 ADJOURNMENT.

SECOND GENERAL SESSION

Monday Evening, April 20, 1942

Presiding Officer

James E. Paullin, F.A.C.P., Atlanta, Ga.

p.m.
8:00 The Leaven of Psychosomatic Medicine.
EDWARD A. STRECKER, F.A.C.P., Professor of Psychiatry, University of Pennsylvania School of Medicine and Graduate School of Medicine, Philadelphia, Pa.
8:30 Is the Art of Physical Diagnosis Being Neglected in Modern Medical Education?
G. GILL RICHARDS, F.A.C.P., Visiting Physician, Dr. W. H. Groves Latter-Day Saints Hospital, Salt Lake City, Utah.
8:50 Specific Stimulating Substances in the Urine of Patients with Myelogenous Leukemia.
JOSEPH T. WEARN, F.A.C.P., Professor of Medicine, Western Reserve University School of Medicine, Cleveland, Ohio.
9:10 Leukemia: The Relative Incidence of Its Various Forms, and Their Response to Radiation Therapy.
FRANK H. BETHELL, F.A.C.P., Assistant Professor of Internal Medicine, University of Michigan Medical School, Ann Arbor, Mich.
9:30 ADJOURNMENT.

10:00 o'Clock

SMOKER

Stem Hall, Municipal Auditorium

A diverting and amusing program has been arranged. See announcement under "Special Features." Admission by registration badge.

THIRD GENERAL SESSION

Tuesday Afternoon, April 21, 1942

Presiding Officer

D. Sclater Lewis, F.A.C.P., Montreal, P. Q.

p.m.
2:00 The Use of Radioactive Elements in Biology and Medicine.
WILLIAM J. KERR, F.A.C.P., Professor of Medicine;
JOHN H. LAWRENCE (by invitation), Assistant Professor of Medicine and Research Associate in the Radiation Laboratory;
JOSEPH G. HAMILTON (by invitation), Clinical Instructor in Neurology and Research Associate in the Radiation Laboratory.

(This paper is from the Department of Medicine, University of California Medical School, San Francisco, and the Crocker Radiation Laboratory, University of California, Berkeley, Calif.)

2:45 Clinical Studies on the Prevention of Venous Thrombosis and Pulmonary Embolism by the Use of a Preparation from Spoiled Sweet Clover Which Prolongs Coagulation and Prothrombin Time of the Blood.
EDGAR V. ALLEN, F.A.C.P., Associate Professor of Medicine, University of Minnesota (Mayo Foundation); Head of a Division of Medicine, Mayo Clinic; Rochester, Minn.
N. W. BARKER, F.A.C.P., Associate Professor of Medicine, University of Minnesota (Mayo Foundation); Consultant in Medicine, Mayo Clinic; Rochester, Minn.

3:05 Embolism of the Popliteal Artery: Its Diagnosis and Treatment.
JOSEPH C. DOANE, F.A.C.P., Clinical Professor of Medicine, Temple University School of Medicine; Associate Professor of Medicine, University of Pennsylvania Graduate School of Medicine; Medical Director, Jewish Hospital; Philadelphia, Pa.

3:25 The High Fluid Intake in the Management of Edema, Especially Cardiac Edema.
F. R. SCHEMM, F.A.C.P., Great Falls, Mont.

3:45 INTERMISSION.

4:05 Newer Knowledge Concerning the Effects of Kidney Extracts on Hypertensive Patients.
IRVINE H. PAGE (Associate, A.C.P.), Director of Clinical Research, Eli Lilly and Company, Indianapolis, Ind.

4:25 Circulatory Disturbances Associated with Prostatic Hypertrophy.
MEREDITH MALLORY, F.A.C.P., Chief of Medical Services;
FRED MATHERS, F.A.C.P., Associate Attending Physician;
LOUIS M. ORR, F.A.C.S. (by invitation), Chief of Urological Service; and
PALMER R. KUNDERT, F.A.C.S. (by invitation), Urological Service; Orange General Hospital, Orlando, Fla.

4:45 The Fraudulent Use of Digitalis to Simulate Heart Disease.
O. F. HEDLEY, F.A.C.P., U. S. Public Health Service, Bethesda, Md.

5:00 ADJOURNMENT.

FOURTH GENERAL SESSION

Wednesday Afternoon, April 22, 1942

Presiding Officer

Jonathan C. Meakins, F.A.C.P., Montreal, P. Q.

COMMUNICABLE DISEASES

p.m.

2:15 Poliomyelitis Virus and Flies.
JOHN R. PAUL (by invitation), Associate Professor of Medicine, Yale University School of Medicine, New Haven, Conn.

2:35 A Comparison of Experimental Poliomyelitis in Several Varieties of Monkeys.
JAMES D. TRASK (by invitation), Associate Professor of Pediatrics, Yale University School of Medicine, New Haven, Conn.

2:55 Typhus Fever.
JOHN S. SNYDER (by invitation), The Rockefeller Institute, International Health Foundation, New York, N. Y.

3:15 Newer Knowledge Concerning the Inception of Pneumonia and Its Bearing on Prevention.
OSWALD H. ROBERTSON (by invitation), Professor of Medicine, University of Chicago, The School of Medicine, Chicago, Ill.

3:40 INTERMISSION.

4:00 The Army's New Frontiers in Tropical Medicine.
LT. COL. JAMES S. SIMMONS, (MC), U. S. Army, F.A.C.P., Chief, Division of Preventive Medicine, Office of the Surgeon General, Washington, D. C.

4:20 Considerations of the Malaria Problem on the Basis of Current Investigations.
LOWELL T. COGGESHALL (by invitation), Professor of Epidemiology, University of Michigan School of Public Health, Ann Arbor, Mich.

4:40 Resurvey of Underlying Factors in Tuberculosis.
THEODORE L. BADGER, F.A.C.P., Instructor in Medicine, Harvard Medical School; Research Fellow, Thorndike Memorial Laboratories, Boston City Hospital; Boston, Mass.

5:00 ADJOURNMENT.

ANNUAL CONVOCATION

Wednesday Evening, April 22, 1942

8:30 o'Clock

Theater, St. Paul Municipal Auditorium

All members of the profession and the general public are cordially invited. No special admission tickets required.

1. The President's Address.
   Roger I. Lee.
2. Presentation of Newly-elected Fellows and Recital of the Pledge.
   George Morris Piersol, Secretary-General.
3. Presentation of the John Phillips Memorial Medal for 1941–42.
4. Announcement of Research Fellows of the College for 1942.
5. Convocational Address: A Consideration of the Factor of Change in the Animal Organism.
   WILLIAM DEB. MACNIDER, F.A.C.P., Kenan Research Professor of Pharmacology, University of North Carolina School of Medicine, Chapel Hill, N. C.

President's Reception

The Reception and Dance will follow one-half hour after the completion of this program, and will be held in the Ballroom (mezzanine floor) of the Hotel Lowry. A cordial invitation is issued to all members and guests, with their families. Newly-inducted Fellows should sign the Roster and secure their Fellowship Certificates during the Reception at the Hotel Lowry.

FIFTH GENERAL SESSION

Thursday Afternoon, April 23, 1942

Presiding Officer

William D. Stroud, F.A.C.P., Philadelphia, Pa.

p.m.

2:00 Definition of the Criteria of an Acceptable Operation for Ulcer.
OWEN WANGENSTEEN (by invitation), Professor of Surgery, University of Minnesota Medical School, Minneapolis, Minn.

2:20 Ileostomy for Chronic Ulcerative Colitis; an Analysis of Results in One Hundred Eighty-five Cases.
J. ARNOLD BARGEN, F.A.C.P., Associate Professor of Medicine, University of Minnesota (Mayo Foundation) and Consultant in Medicine, Mayo Clinic, Rochester, Minn.;
W. W. LINDAHL (by invitation), Fellow in Medicine, Mayo Foundation, Rochester, Minn.;
FRANK ASHBURN (by invitation), Fellow in Surgery, Mayo Foundation, Rochester, Minn.

2:40 Discussion of the Nature of the Hyperglycemia of the Obese Middle-Aged Person.
L. H. NEWBURGH, F.A.C.P., Professor of Clinical Investigation, University of Michigan Medical School, Ann Arbor, Mich.

3:00 New Trends in Treatment of Chronic Disease; an Experience in Spa Therapy.
WALTER S. MCCLELLAN (by invitation), Associate Professor of Medicine, Albany Medical College, Saratoga Springs, N. Y.

3:20 The Mediaeval Physician.
JABEZ H. ELLIOTT, F.A.C.P., Professor of History of Medicine, University of Toronto Faculty of Medicine, Toronto, Ont.

3:45 INTERMISSION.

4:00 Pertinent Problems of Geriatric Medicine.
EDWARD J. STIEGLITZ, F.A.C.P., Research Associate in Charge of Investigations in Gerontology, National Institute of Health, Washington, D. C.

4:20 Factors which May Influence Senescence.
NATHAN S. DAVIS, III, F.A.C.P., Assistant Professor of Medicine, Northwestern University Medical School, Chicago, Ill.

4:40 ADJOURNMENT, to be followed immediately by

THE ANNUAL BUSINESS MEETING

All Masters and Fellows are urged to be present. Annual reports of the Secretary-General, Executive Secretary and Treasurer will be presented; new Officers, Regents and Governors will be elected, and the President-Elect, Dr. James E. Paullin, Atlanta, Ga., will be inducted into office.

THE ANNUAL BANQUET OF THE COLLEGE

Thursday Evening, 8:00 o'Clock

Ballroom, Hotel Lowry

(Procure tickets at the Registration Bureau)
Consult Special Banquet Program

Toastmaster: John A. Lepak, F.A.C.P., St. Paul, Minn.
Address: "Medicine and the Public."
William A. O'Brien, Director of Postgraduate Medical Education, University of Minnesota, Minneapolis, Minn.

SIXTH GENERAL SESSION

Friday Afternoon, April 24, 1942

Presiding Officer

George Morris Piersol, F.A.C.P., Philadelphia, Pa.

p.m.

2:15 The Clinical Significance of Pyuria.
WILLIAM F. BRAASCH (by invitation), Professor of Urology, University of Minnesota (Mayo Foundation), Rochester, Minn.

2:35 Penicillin as a Chemo-therapeutic Agent.
M. HENRY DAWSON (by invitation), Associate Professor of Medicine, Columbia University College of Physicians and Surgeons, New York, N. Y.

2:55 Gramicidin in the Treatment of Local Infections.
CHESTER S. KEEFER, F.A.C.P., Wade Professor of Medicine, Boston University School of Medicine, Boston, Mass.

3:15 Primary Coccidiodomyocosis.
WILLIAM A. WINN (Associate, A.C.P.), Superintendent and Medical Director, Tulare-Kings Counties Joint Tuberculosis Hospital, Springville, Calif., and
GILBERT JOHNSON (by invitation), Springville, Calif.

3:35 The Effectiveness of Replacement Therapy in Achlorhydria.
ALFRED E. KOEHLER (Associate, A.C.P.), Sansum Clinic, Santa Barbara, Calif.

3:55 Ten Years' Experience with Thorotrast Hepatosplenography.
WALLACE M. YATER, F.A.C.P., Professor of Medicine, Georgetown University School of Medicine, Washington, D. C.

4:10 A Recent Advance in the Treatment of Gout.
ELMER C. BARTELS, F.A.C.P., Physician, New England Deaconess and New England Baptist Hospitals, Boston, Mass.

4:30 ADJOURNMENT.

GENERAL SESSIONS

IF TIME PERMITS

Studies on Induced Auricular Fibrillation with Quinidine, Hydroquinidine, and "Pure Quinidine."
S. A. WEISMAN, F.A.C.P., Clinical Assistant Professor of Medicine, University of Minnesota Medical School, Minneapolis, Minn.

Observations on the Effects of Combined Fever and X-Ray Therapy in the Treatment of Malignancy.
EDWARD L. TURNER, F.A.C.P., Dean and Professor of Medicine, Meharry Medical College, Nashville, Tenn.;
HEDDY S. SHOULDERS (by invitation), Professor of Radiology, Meharry Medical College, Nashville, Tenn.; and
LAWRENCE D. SCOTT (by invitation), Assistant Professor of Radiology, Meharry Medical College, Nashville, Tenn.

Blood Pressure and Sulfocyanates.
VERNE S. CAVINESS, F.A.C.P., Assistant Chief of Medical Staff, Rex Hospital, Raleigh, N. C.;
THOMAS L. UMPHLET (Associate, A.C.P.), Attending Physician, Rex Hospital, Raleigh, N.C.; and

CHAUNCEY L. ROYSTER (by invitation), Associate Physician, Rex Hospital, Raleigh, N. C.

Potential Health Hazards in a Changing Social and Economic World.

F. GORHAM BRIGHAM, F.A.C.P., Physician-in-Chief, Palmer Memorial and New England Deaconess Hospitals, Boston, Mass.

Medical Education after Graduation.

HUGH J. MORGAN, F.A.C.P., Professor of Medicine, Vanderbilt University School of Medicine, Nashville, Tenn.

Orientation of Treatment in Thrombophlebitis, Phlebothrombosis and Pulmonary Embolism.

JAMES A. EVANS, F.A.C.P., Physician, Medical Department, Lahey Clinic, Boston, Mass.

MORNING LECTURES

The Morning Lectures are in response to increasing interest in fundamental problems and are planned to relate as closely as possible to the subject matter of the General Sessions.

They will be held daily, Tuesday through Friday, from 9:30 to 11:30 a.m., in the Theater of the Municipal Auditorium.

The lectures will be open to all members and guests of the College.

Admission by regular registration badge.

Tuesday, April 21, 1942

Theater, Municipal Auditorium

Presiding Officer

Thomas T. Holt, F.A.C.P., Wichita, Kan.

a.m.

9:30–10:30 The Plans of the Army and Navy for Treatment of Shock.
G. CANBY ROBINSON (by invitation), Lecturer in Medicine and Lecturer in Preventive Medicine, Johns Hopkins University School of Medicine, Baltimore, Md.

10:30–11:30 Blood Proteins.
EDWIN J. COHN (by invitation), Professor of Biological Chemistry, Harvard Medical School, Boston, Mass.

Wednesday, April 22, 1942

Theater, Municipal Auditorium

Presiding Officer

Samuel E. Munson, F.A.C.P., Springfield, Ill.

a.m.

9:30–10:30 The Male Hormones.
ALLAN T. KENYON (by invitation), Assistant Professor of Medicine, University of Chicago, The School of Medicine, Chicago, Ill.

10:30–11:30 The Female Hormones.
ELMER L. SEVRINGHAUS, F.A.C.P., Professor of Medicine, University of Wisconsin, Medical School, Madison, Wis.

Thursday, April 23, 1942

Theater, Municipal Auditorium

Presiding Officer

T. Homer Coffen, F.A.C.P., Portland, Ore.

a.m.

9:30–10:30 The Use of Heat in Therapeutics.
STAFFORD L. WARREN (by invitation), Professor of Radiology, University of Rochester School of Medicine and Dentistry, Rochester, N. Y.

10:30–11:30 The Use of Cold in Medicine.
LAWRENCE W. SMITH (by invitation), Professor of Pathology, Temple University School of Medicine, Philadelphia, Pa.

Friday, April 24, 1942

Theater, Municipal Auditorium

Presiding Officer

Gerald B. Webb, F.A.C.P., Colorado Springs, Colo.

a.m.

9:30–10:30 Epilepsy.
WILLIAM G. LENNOX (by invitation), Assistant Professor of Neurology, Harvard Medical School, Boston, Mass.

10:30–11:30 A Review of the Drastic Therapies of the Psychoses.
FRANKLIN G. EBAUGH (by invitation), Professor of Psychiatry, University of Colorado School of Medicine, Denver, Colo.

PANEL DISCUSSIONS

The Panel Discussions embrace not only timely subjects, but also topics of the greatest interest and practical nature to the profession. Care has been taken to avoid too many duplications with topics discussed within recent years, yet where a subject has remained perennially fresh, it has not been omitted. Only highly qualified men in their respective fields have been chosen as leaders of the Panel Discussions and they in turn have selected their own personnel. For the most part the discussers have been gathered from all parts of the country in order to secure the best talent available for each Panel. In three instances, however, the chief of a department at the University of Minnesota, for the sake of better teamwork, preferred to take his own departmental associates, representing various phases of the subject, along into the Panel Discussion. Under such circumstances the listeners should be able to receive the latest as well as the most orthodox views and opinions on the subject under discussion.

The Panel Discussions will be held in the Municipal Auditorium from 12:00 m. to 1:15 p.m. daily—Tuesday through Friday.

When application is made for tickets, it is suggested that the applicant submit in writing any question or phase of the subject which he especially wishes discussed. Questions may also be submitted at least twenty-four hours before the discussion to the General Chairman. A certain number of these request questions may not be answered on account of the lack of time. Leaders will answer those questions which seem to be most in demand.

Members should make application for Panel Tickets on the regular application form accompanying the formal program, or at the Registration Bureau at the Municipal Auditorium.

PANEL DISCUSSIONS—12:00 M.-1:15 P.M.

Tuesday April 21	PERIPHERAL VASCULAR DISEASES INCLUDING HYPERTENSION *Edgar V. Allen Irving S. Wright I. H. Page	HEMATOLOGY *H. Z. Giffin F. J. Heck F. J. Hirschboeck	ELECTROCARDIOGRAPHY *A. R. Barnes Harold Feil Edgar Hull Frank N. Wilson	TRAUMATIC LESIONS OF THE CENTRAL NERVOUS SYSTEM *Ernest M. Hammes W. H. Hengstler George Ruhberg	ACUTE AND CHRONIC TYPES OF ARTHRITIS *Philip S. Hench Richard H. Freyberg Russell L. Cecil
Wednesday April 22	TREATMENT OF GLOMERULONEPHRITIS *Moses Barron Norman M. Keith Louis Leiter	GERIATRICS—THE MEDICAL PROBLEM OF OUR ADVANCING AGE GROUP *E. L. Tuohy W. C. Alvarez Edward J. Stieglitz	VITAMIN ADMINISTRATION IN PREVENTION AND TREATMENT OF DEFICIENCY DISEASES *Russell M. Wilder Hugh R. Butt Norman Jolliffe	PEDIATRICS AND CONTAGIOUS DISEASES *Irvine McQuarrie E. J. Huenekens E. S. Platou	ORGANIC AND FUNCTIONAL DISORDERS OF THE UPPER DIGESTIVE TRACT, SMALL BOWEL AND COLON *George B. Eusterman J. B. Carey E. G. Wakefield
Thursday April 23	THE ALLERGIC DISEASES *R. V. Ellis Elmer M. Rusten Asher A. White Albert V. Stoesser	PRACTICAL USES OF ENDOCRINE SUBSTANCES *Max Hoffman Elmer L. Sevringhaus E. H. Rynearson Willard O. Thompson	TUBERCULOSIS *J. A. Myers C. A. Stewart S. A. Slater	CORONARY INSUFFICIENCY—DIAGNOSIS AND TREATMENT OF ANGINA PECTORIS AND CORONARY OCCLUSION *S. Marx White Wm. J. Kerr Fred M. Smith	TREATMENT OF LOBAR PNEUMONIA *George E. Fahr Jonathan C. Meakins Francis G. Blake
Friday April 24	HEART DISEASES *Fredrick A. Willius R. Wesley Scott William D. Stroud	VIRUS DISEASES OF THE NERVOUS SYSTEM *J. C. McKinley Robert Green A. B. Baker	DISEASES OF THE LIVER AND BILIARY TRACT *Cecil J. Watson T. L. Althausen J. L. Bollman	PROBLEMS CONCERNING THE CLINICAL USE OF SULFANILAMIDE AND RELATED COMPOUNDS *Wesley W. Spink Alex. E. Brown Edwin G. Bannick	INDICATIONS AND CONTRA-INDICATIONS, OR USES AND ABUSES OF INTRAVENOUS THERAPY *Henry L. Ulrich Gerald Evans John Anderson

* Chairman.

CLINICS AND DEMONSTRATIONS

9:00 to 11:30 a.m.

Tuesday, Wednesday, Thursday and Friday

April 21–24, 1942

Clinics will be held in five St. Paul hospitals and two amphitheaters in the Medical School of the University of Minnesota. Each clinical morning will begin promptly at 9:00 o'clock and end with equal promptness at 11:30 in order to allow plenty of time for those who wish to reach the Panel Discussions. To avoid congestion in some and a greatly reduced attendance in other hospitals, registration and tickets will be required for clinics. After each clinic ten minutes will be allowed for questions and answers. Daily clinics will be held in the following hospitals:

Name of Hospital	*Capacity*
University Hospital, University of Minnesota Medical School	
412 S. E. Delaware Ave., Minneapolis, Minn.	
A-1 Todd Amphitheater	150
A-2 Medical Science Bldg., Amphitheater, Room 15	350
Ancker Hospital	
495 Jefferson Ave., St. Paul, Minn.	
B-1 West Ward, First Floor	350
B-2 Auditorium	150
St. Luke's Hospital	
287 Smith Ave., St. Paul, Minn.	
C-1 Nurses' Auditorium	200
C-2 Nurses' Recreation Hall	100
St. Joseph's Hospital	
69 N. Exchange St., St. Paul, Minn.	
D-1 Auditorium	200
D-2 New Lecture Hall	200
Charles T. Miller Hospital, Inc.	
125 W. College Ave., St. Paul, Minn.	
E-1 Staff Meeting Hall	80
E-2 Nurses' Auditorium	100
Bethesda Hospital	
559 Capitol Blvd., St. Paul, Minn.	
F Auditorium	150

Hospitals participating, but not holding clinics are:

Children's Hospital, Inc., 311 Pleasant Ave., St. Paul, Minn.
Gillette State Hospital for Crippled Children, 1003 Ivey Ave., St. Paul, Minn.
Midway Hospital, 1700 University Ave., St. Paul, Minn.
Mounds Park Hospital, 200 Earl Ave., St. Paul, Minn.
Northern Pacific Hospital, 1515 Charles Ave., St. Paul, Minn.
St. John's Hospital, 390 Mounds Blvd., St. Paul, Minn.

Each individual clinician will give the history of the patient he presents, demonstrate the physical findings, enumerate the laboratory data, arrive at his own diagnosis, outline the course of treatment and finally discuss the prognosis. In the time allotted, it is expected that the clinician will present at least two patients. Such a procedure should prove undeniably instructive, practical and clinical in nature.

For physicians not especially interested in clinics, but more absorbed in clinical-pathological correlation or the interpretation of certain laboratory findings and

procedures, there will be set aside each morning a delightful program at St. Joseph's Hospital in the New Lecture Hall. The morning exercises will be divided into two parts. The first part will consist of a demonstration of unusual roentgen-ray pictures, discussion of eye grounds in various diseases illustrated by colored drawings, demonstration of a great variety of dermatological conditions with colored slides, and finally the evaluation of a blood sedimentation test as a part of the routine health examination of young adults. The second part will consist of a clinical-pathological conference. A case report will be forwarded to each clinician selected to lead the conference. This report will be analyzed by the clinician at the conference to establish the diagnosis. The diagnosis will, then, either be confirmed or disapproved by the pathologist. Reports of the case under discussion will also be furnished to the audience.

If any one wishes, however, to secure case histories for study before the conference, he may obtain them by notifying

HAROLD EDWARD RICHARDSON, M.D.,
Chairman on Clinics,
1154 Lowry Medical Arts Bldg.,
St. Paul, Minn.

UNIVERSITY AND SAINT PAUL HOSPITALS

TRUE to its pioneering traditions, St. Paul has led the way in Minnesota in the establishment of hospitals. First city in the state to have such an institution, St. Paul today boasts twelve modern, well-equipped hospitals, five of which will be the scene of clinics to be conducted during the annual meeting of the American College of Physicians. Also participating will be the University of Minnesota Hospital in Minneapolis. All the hospitals conducting clinics are approved for standardization by the American College of Surgeons; approved for general internship by the American Medical Association, and are members of the American Hospital Association.

St. Joseph's Hospital. (Figure 1.) It was 89 years ago—1853—that the Sisters of St. Joseph of Carondelet, acting at the instigation of the then Bishop Cretin, founded St. Joseph's Hospital. St. Paul was then a wild frontier territory, inhabited by warring bands of Sioux and Chippewa Indians. A hospital was sorely needed when in the fall of 1853 construction was begun on the four-story stone building. A year later it was completed, becoming the first institution for the care of the sick and wounded in the Minnesota territory. One dollar a day was the charge at that time for the care of patients.

Most noteworthy and historic achievement in St. Joseph's history occurred on September 24, 1886, when the first cholecystectomy ever done in America was performed by Dr. Justus Ohage, Sr. The patient withstood the operation well and remained in good health for fifty years.

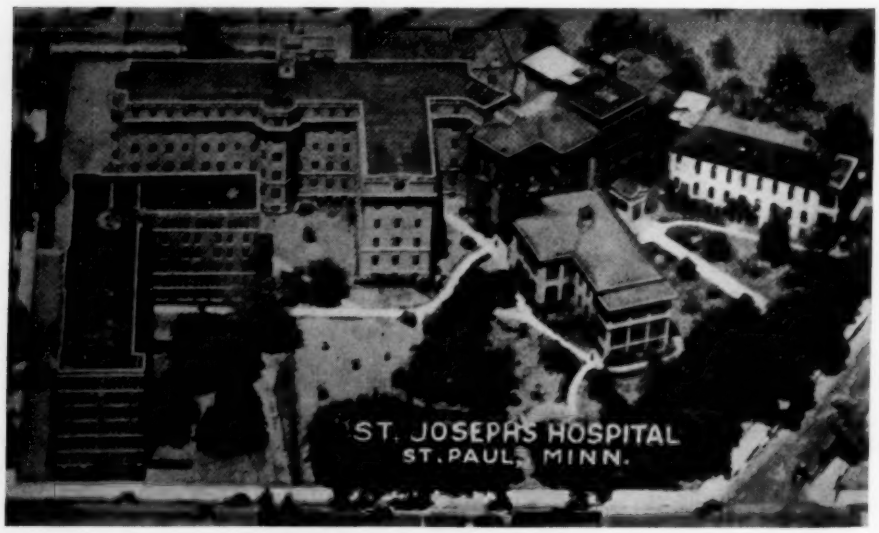


FIG. 1. ST. JOSEPH'S HOSPITAL.

FIG. 2. ANCKER HOSPITAL.

Today St. Joseph's is a modern general hospital with services in general medicine, general surgery, cancer, dermatology, diabetes, gynecology, some neurology, obstetrics, ophthalmology, orthopedics, otolaryngology, pediatrics, some psychiatry, syphilis and urology. Contagious diseases and tuberculosis are not admissible cases. Special departments include a school of nursing, dietetic, roentgen-ray, clinical and pathological laboratories, physical therapy and electrocardiography. St. Joseph's has 240 beds and 24 bassinets.

Ancker Hospital. (Figure 2.) Ancker Hospital, established in 1872 as the "City and County Hospital," had its name changed in 1923 in honor of Arthur B. Ancker, M.D., who served the institution from 1883 to 1923 as superintendent and physician and surgeon. The hospital is approved by the American College of Surgeons for graduate training in general surgery, urology, obstetrics and gynecology, ophthalmology and otolaryngology.

Owned by the City of St. Paul and Ramsey County, and controlled by a board of public welfare, Ancker Hospital provides services in general medicine, general surgery, cancer, contagious diseases, dermatology, diabetes, gynecology, neurology, obstetrics, ophthalmology, orthopedics, otolaryngology, pediatrics, psychiatry, syphilis, all stages of tuberculosis in any form, and urology.

Special departments at Ancker include outpatient, school of nursing, social service, dietetic, occupational therapy, electrocardiograph, postgraduate school of nursing, roentgen-ray, clinical and pathological laboratories. Capacity is 1,000 beds and 50 bassinets. Ancker is a teaching hospital affili-

FIG. 3. BETHESDA HOSPITAL.

FIG. 4. THE CHARLES T. MILLER HOSPITAL.

FIG. 5. ST. LUKE'S HOSPITAL.

ated with the University of Minnesota Medical School. It is approved for general internship and residency in a specialty by the American Medical Association.

The hospital provides a rotating internship of one year's duration. The resident usually is selected from the intern group of the hospital. The plan of training in general surgery includes also orthopedic surgery and fractures. The first six months of training is in the department of pathology, with the next twelve devoted to orthopedic surgery and fractures. During the final eighteen months of training the resident has complete charge of the general surgical services.

Bethesda Hospital. (Figure 3.) St. Paul's newest, originally was founded fifty-nine years ago by the Lutheran Minnesota Conference of the Augusta Synod through the efforts of the Rev. A. P. Monten, pastor of the First Lutheran Church, St. Paul. It began in a private dwelling April 4, 1882, and continued for ten months, when it was discontinued for lack of

proper facilities. In 1891 reorganization was instituted by the Conference and a year later the hospital reopened in a new location. The present building, located behind the Minnesota State Capitol, was completed and dedicated October 2, 1932.

A general hospital, Bethesda affords services in general medicine, general surgery, cancer, diabetes, gynecology, neurology, obstetrics, ophthalmology, orthopedics, some pediatrics, syphilis, and urology. Contagious and mental cases are not admitted. Special departments are outpatient, school of nursing, dietetic, roentgen-ray, clinical and pathological labora-

FIG. 6. UNIVERSITY OF MINNESOTA, MEDICAL CAMPUS, 1941.

1. Medical Sciences Building
2. College of Dentistry
3. School of Medicine
4. School of Nursing
5. Millard Hall
6. Preventive Medicine and Public Health
7. Department of Medicine
8. Physiology
9. Bacteriology and Immunology
10. Pharmacology
11. Institute of Anatomy
12. Anatomy
13. Pathology
14. Students' Health Service
15. Interns Quarters
16. Child Psychiatry
17. Obstetrics and Gynecology
18. Orthopedic Surgery
19. Outpatient Department
20. Eustis Hospital
21. Pediatrics
22. Diagnostic Roentgenology
23. Dermatology
24. Urology
25. Anesthesiology
26. Elliot Memorial Hospital
27. Laboratory Service
28. Hospital Administration
29. Psychopathic Unit
30. Surgery
31. Neurosurgery
32. Cancer Institute
33. Radiation Therapy
34. Todd Memorial Hospital
35. Internal Medicine
36. Ophthalmology and Otolaryngology
37. Louise M. Powell Hall for Nurses
38. Pioneer Hall for Men
39. Botany
40. Zoology

FIG. 8. GILLETTE STATE HOSPITAL.

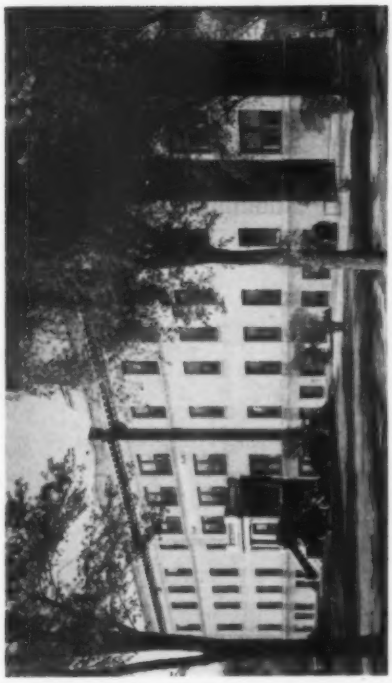


FIG. 10. MOUNDS PARK HOSPITAL.

FIG. 7. THE CHILDREN'S HOSPITAL.

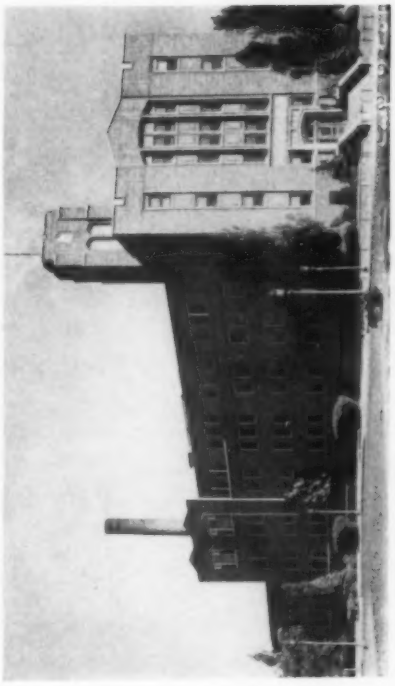


FIG. 9. MIDWAY HOSPITAL.

tories, physical therapy and electrocardiography. Capacity, 110 beds, 14 bassinets.

Miller Hospital. (Figure 4.) The Charles T. Miller Hospital, a non-profit endowed institution, was opened December 1, 1920—the realization of the dreams and wishes of the late Charles Terry Miller, native of Jacksonville, Ill., who came to St. Paul as a young man and acquired a fortune. Mr. Miller died in 1910 and his widow provided a bequest of $1,400,000 to carry out her husband's wish to endow a hospital. Her will stipulated that 50 free beds be maintained for indigent patients without regard to race, creed or color.

Miller Hospital departments include outpatient, school of nursing, social service, dietetic, physical and occupational therapy, electrocardiography, post-graduate school of nursing, organized library, roentgen-ray, clinical and pathological laboratories.

An outstanding feature of the hospital is its excellent diagnostic, chemical, serological and biological laboratory under the supervision of a full-time pathologist. Through an affiliation with Macalester College, six students are received each year for training as laboratory technicians.

In 1937 a specially constructed addition was built to house a 1,200 kilovolt roentgen-ray machine for deep therapy treatment. This machine was built to yield radiation approaching the gamma rays of radium in penetration and quality. It is one of the comparatively few installations in the country which produces such radiation.

Since 1923 Miller Hospital has been affiliated with the Amherst H. Wilder Dispensary, whose buildings adjoin the hospital. The dispensary serves as the outpatient department of the hospital and is the source of the hospital's free patients.

A general hospital, Miller's services include general medicine, general surgery, cancer, dermatology, diabetes, gynecology, neurology, obstetrics, ophthalmology, orthopedics, otolaryngology, pediatrics, syphilis, tuberculosis, and urology.

St. Luke's Hospital. (Figure 5.) Like St. Joseph's Hospital, St. Luke's was founded before Minnesota was admitted to the Union—in 1857. It was opened originally as an Episcopalian institution under the name, "Christ Church Hospital and Orphan Home for Minnesota." Its present name dates from 1877. The late General Henry Hastings Sibley, noted pioneer, territorial delegate to Congress and governor when Minnesota was admitted to the Union, served as president of the hospital board from 1873 until his death in 1890.

St. Luke's Hospital provides services in general medicine, general surgery, cancer, dermatology, diabetes, gynecology, neurology, obstetrics, ophthalmology, orthopedics, otolaryngology, syphilis, and urology. Mental and contagious cases are not admissible. Departments: school of nursing.

FIG. 11. NORTHERN PACIFIC HOSPITAL.

FIG. 12. ST. JOHN'S HOSPITAL.

FIG. 13. WEST SIDE GENERAL HOSPITAL.

diabetic, physical therapy, electrocardiography, organized library, and roentgen-ray, clinical and pathological laboratories.

University Hospital. (Figure 6.) The Minnesota General Hospital (University of Minnesota Medical Center), as its name implies, provides general services in medicine, surgery, cancer, dermatology, diabetes, gynecology, neurology, obstetrics, ophthalmology, orthopedics, otolaryngology, pediatrics, tuberculosis (surgery only), and urology. Contagious and mental diseases and active tuberculosis cases are not admitted.

University Hospital, as the institution is commonly known, was erected in 1911 through the generosity of Adolphus S. Elliot, M.D., and until 1921 was known as Elliot Memorial Hospital as a part of the University of Minnesota. In addition to Elliot Hospital, the University Medical Center comprises the Todd Hospital for the care of eye, ear, nose and throat cases, Eustis Hospital for children and the Memorial Cancer Institute.

The Mayo brothers, William J. and Charles H., both now deceased, played an important part in the development of the University of Minnesota Medical School and the University Hospitals. On February 9, 1915, they founded the Mayo Foundation for Medical Education and Research, entering into an agreement by the terms of which the funds and income of the foundation are devoted, under direction of the University Board of Regents, to the promotion of graduate work in medicine and to research in this field. On September 13, 1917, funds and income of the Mayo Foundation were transferred entirely to the Regents of the University.

Under terms of a Minnesota statute any legal resident of the state "afflicted with a malady, deformity or ailment of a nature which can probably be remedied by hospital service and treatment, and is unable financially to pay for same, is entitled to admission to the 'Minnesota General Hospital.'" Public officials refer probable patients to the hospital and after necessary blanks are filled out, and county commissioners have given their approval, admission is granted. The hospital prefers needy patients with a "teaching value."

Other St. Paul hospitals, in addition to those in which clinics are to be conducted, are Children's Hospital (Figure 7), Gillette State Hospital (Figure 8), Midway Hospital (Figure 9), Mounds Park Hospital (Figure 10), Northern Pacific Hospital (Figure 11), St. John's Hospital (Figure 12), and the West Side General Hospital (Figure 13).